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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Patent of

Jean-Pierre KAPLAN et al.

U.S. Patent No. 4,382,938

Issued: May 10, 1983

Serial No. 313,601 Group Art Unit: *

Filed: October 21, 1981 Examiner: H. Jiles

For: IMIDAZO[1,2-a]PYRIDINE DERIVATIVES AND THEIR APPLICATION AS PHARMACEUTICALS

MAIL ROOM JAN 25 1993 PAT. & TRADEMARK OFF. 20

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LETTER ACCOMPANYING APPLICATION FOR EXTENSION

BOX PAT. EXT.
Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

Enclosed herewith is a REQUEST FOR EXTENSION OF PATENT TERM for filing as of this date; kindly also make of record the following:

FEES FOR AMENDED CLAIMS

Excess independent claims at $72 each - ___	$_____
Excess total claims at $20 each -	$_____
First multiple dependent claim at $220 extra -	$_____

EXTENSION OF TIME PETITION

If this paper is filed outside the regular shortened period for response, applicant(s) petition(s) for the minimum extension of time needed to effect timely filing of the instant paper, calculated as being for a total of _____ month(s), and the fee being	$_____
EXTENSION OF TERM OF PATENT FEE	$1,000.00
[X] TOTAL FEE: Our check is included for:	$1,000.00

[X] Applicant(s) generally authorize(s) payment of any required fee for the filing of this paper (even if different from any calculation above) to our Deposit Account 23-0783 under our general authorization under 37 CFR 1.17.

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Atty. Doc.: 8550-5480
DATE: January 25, 1993
DPM:ldc/2.7250 MS 02/17/93 4382938

Respectfully submitted,

Douglas P. Mueller
Reg. No. 30,300

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Patent of

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For: IMIDAZO[1,2-a]PYRIDINE DERIVATIVES AND THEIR APPLICATION AS PHARMACEUTICALS

REQUEST FOR EXTENSION OF PATENT TERM

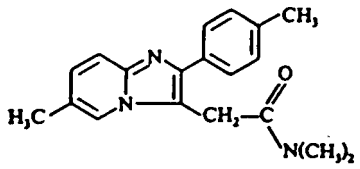
Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

Synthelabo, owner by Assignment (Reel 3941, Frame 0248) of U.S. Patent No. 4,382,938, requests that the term of U.S. Patent No. 4,382,938 be extended for a period of five years. The information required by 37 CFR 1.740 is set forth below.

1. IDENTIFICATION OF THE APPROVED PRODUCT

The approved product will be marketed under the tradename AMBIEN, and is a sedative/hypnotic agent. Filed herewith is the approved labelling for AMBIEN. The active ingredient in AMBIEN is the imidazo[1,2-a] pyridine compound known as zolpidem. Specifically, zolpidem tartrate is the salt form of zolpidem used in AMBIEN. Zolpidem has the following structural formula:



2. IDENTIFICATION OF THE PROVISION OF LAW UNDER WHICH REGULATORY REVIEW OCCURRED

FDA review of AMBIEN took place under Section 505(b) of the Federal Food, Drug and Cosmetic Act.

3. IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE

FDA approval for AMBIEN was granted on December 16, 1992.

4. IDENTIFICATION OF ACTIVE INGREDIENTS IN AMBIEN

Zolpidem tartrate is the sole active ingredient in AMBIEN. This is the first approval of zolpidem, or any salt or ester thereof.

5. STATEMENT OF SUBMISSION WITHIN A 60-DAY PERIOD

It is confirmed that this application is being submitted within 60 days following the approval of AMBIEN, the 60-day period expiring on February 14, 1993.

6. IDENTIFICATION OF THE PATENT FOR WHICH EXTENSION IS BEING SOUGHT

Extension is being sought for U.S. Patent No. 4,382,938, which names as inventors Jean-Pierre Kaplan and Pascal George. U.S. Patent No. 4,382,938 issued on May 10, 1983. The full 17-year patent grant is applicable and therefore the date of expiration (assuming the payment of maintenance fees) is May 10, 2000.

7. COPY OF THE PATENT

A copy of U.S. Patent No. 4,382,938 accompanies this application.

8. COPY OF DISCLAIMERS, CERTIFICATES OF CORRECTION, ETC.

Included with the attached copy of U.S. Patent No. 4,382,938 are copies of the receipts for maintenance fee payment for this patent. There have been no disclaimers, certificates of correction or reexamination certificates.

9. CLAIMS READING UPON THE APPROVED PRODUCT

Claims 1-6 of U.S. Patent No. 4,382,938 read upon the approved product or uses therefor. Initially, it is noted that claim 1 is an independent compound claim and claim 4 is an independent use claim directed to a method of providing a hypnotic effect.
The claims of the patent are set up in a parallel fashion. That is, the scope of the compound of claim 1 is identical to the scope of the active agent in independent method claim 4. Each of the

independent claims is provided with two dependent claims, and the dependent claims are identical for each of the independent claims.

Turning to the independent claims, it can be seen that zolpidem has the same basic ring structure as is required in the independent claims. The independent claims require that X_1 be halogen or methyl, with the corresponding substituent of zolpidem being methyl. Y is required to be hydrogen, halogen or methyl, with zolpidem again meeting this requirement through its methyl substituent in the position corresponding to the claimed Y. R_1 is required to be hydrogen, C_{1-5} alkyl or hydroxy (C_{1-5} alkyl). Zolpidem includes a methyl substituent for R_1, i.e., a member of the C_{1-5} alkyl group. R_2 is required to be C_{1-5} alkyl or hydroxy (C_{1-5} alkyl). Again, in zolpidem, the corresponding substituent is methyl. It should be noted that the independent claims permit salt forms.

Dependent claims 2 and 5 require that R_1 and R_2 both be alkyl radicals. In the case of zolpidem, both are methyl and meet the requirement. Dependent claims 3 and 6 depend from claims 2 and 5 and require that Y be chlorine or methyl. In zolpidem, Y is methyl, thereby meeting the requirement of these claims. Claims 4-6 are directed to methods for providing a hypnotic effect, which is the approved use of AMBIEN. Thus, claims 1-6 read on the approved product or a method of using the approved product.

10. EFFECTIVE DATES OF IND APPLICATION AND NDA APPLICATION

The IND was submitted on November 15, 1984 and was assigned No. 25,361. The NDA was submitted on January 26, 1989 and was assigned No. 19,908. The NDA was approved on December 16, 1992.

11. ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT

A summary of the activities undertaken by the marketing applicant during the regulatory review period follows.

IND 25,361
(zolpidem tartrate)

CHRONOLOGY

1984

11/14/84 Phone call to FDA alerting them that an IND submission for zolpidem is coming.

11/15/84 Submission of Original IND for zolpidem.

12/28/84 Phone call from FDA (J. Richman, Reviewing Chemist for zolpidem IND) with questions.

12/03/84 Phone call to FDA (J. Richman) in response to 11/28/84 phone call regarding issues.

12/10/84 Phone call from FDA (D. Cutright, CSO) with request that Lorex not start clinical studies until Lorex hears from them in writing.

12/14/84 Phone call from FDA (D. Cutright) regarding delay in starting clinical trials.

12/17/84 Phone call from FDA (D. Cutright) with details regarding hold on IND and FDA letter to Lorex.

12/21/84 Letter to FDA (Dr. Leber) requesting meeting with Neuropharm to discuss clinical hold.

1985

01/08/85 Phone call to FDA (D. Cutright) to verify FDA's receipt of 12/21/84 letter (Had not received)

01/11/85 Phone call to FDA (D. Cutright) to follow-up on 12/21/84 letter to FDA. (Had not received)

01/16/85 Phone call to FDA (D. Cutright) to follow-up on 12/21/84 letter to FDA. (Had not received)

01/22/85 Visit to FDA to deliver copies of 12/21/84 letter. Discussions with J. Purvis, Supervisory CSO regarding status of FDA letter and Neuropharm policies.

01/23/85 Phone call to FDA (J. Purvis) regarding status of FDA letter to Lorex.

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CHRONOLOGY

02/05/85 Phone call to FDA (D. Cutright) regarding status of FDA letter to Lorex.

02/20/85 Phone call from FDA (D. Cutright) regarding status of FDA letter to Lorex.

02/25/85 Phone call from FDA (D. Cutright) informing Lorex that FDA was prepared to grant our request for a meeting.

02/26/85 Phone call to FDA (D. Cutright) to confirm date of meeting with FDA.

03/14/85 Meeting between Lorex, Synthelabo and FDA to discuss the issues surrounding the 3-month hold on zolpidem IND.

04/23/85 Letter from FDA outlining what information needed to be submitted for their continued review of the zolpidem IND.

04/25/85 Submission of updated information.

04/29/85 Submission of protocol.

05/17/85 Response to FDA letter dated 04/23/85.

06/03/85 Phone call to FDA (D. Cutright) inquiring into status of FDA review of protocol.

06/05/85 Phone call from FDA (D. Cutright) regarding status of protocol review.

06/20/85 Phone call to FDA (D. Cutright) regarding status of protocol review.

06/27/85 Phone call to FDA (D. Cutright) regarding status of protocol review.

07/01/85 Phone call to FDA (D. Cutright) regarding status of protocol review.

07/02/85 Phone from FDA (D. Cutright) regarding status of protocol review.

07/11/85 Phone call from FDA (D. Cutright) giving verbal go-ahead to proceed with the study.

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CHRONOLOGY

07/15/85 Letter from FDA granting approval for Lorex to proceed with protocol.

11/01/85 Submission of Safety Report.

11/15/85 Phone call to FDA (D. Cutright) regarding progress report due date.

11/25/85 Submission of Protocol Amendment.

12/09/85 Submission of Annual Progress Report.

12/17/85 Submission of Annual Progress new protocol.

1986

01/22/86 Phone call from FDA (J. Creamer, CSO) regarding our 12/17/85 submission of protocol.

02/03/86 Resubmission of protocol.

02/06/86 Submission of Safety Report.

04/08/86 Submission of new protocol.

04/17/86 Submission of follow-up information to Safety Report.

04/21/86 Submission of new protocol LSH02.

05/14/86 Submission of Protocol Amendments.

08/27/86 Submission of new protocol.

09/11/86 Submission of new protocol.

10/01/86 Phone call to FDA (J. Creamer) to inquire as to whether a separate IND would be required for the use of zolpidem as a premedicant.

10/07/86 Phone call from FDA (J. Creamer) in response to our 10/01/86 phone call to FDA regarding protocol.

10/10/86 Phone call from FDA (J. Creamer) stating that FDA could not find Lorex's 08/27/86 submission and requesting a second copy be forwarded to her attention.

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CHRONOLOGY

10/13/86 Re-submission of protocol.

10/20/86 Phone call to FDA (J. Creamer).

10/20/86 Phone call to FDA (J. Creamer) inquiring into the status of FDA's review of protocol.

11/03/86 Submission of new protocol.

11/04/86 Submission of Safety Report.

11/10/86 Submission of Protocol Amendment.

11/13/86 Phone call from FDA regarding status of protocol.

11/20/86 Phone call to FDA regarding status of protocol.

11/26/86 Submission of Annual Progress Report.

12/01/86 Submission of new protocol with Amendment.

12/04/86 Phone call to FDA regarding status of protocol.

12/15/86 Submission of new protocol with Amendment.

12/18/86 Phone call to FDA regarding status of protocol.

1987

01/13/87 Phone call to FDA regarding status of protocol.

01/26/87 Submission of new protocol LSH11 with Amendment.

01/27/87 Submission of new investigator for protocol.

01/29/87 Submission of CMC Amendment.

02/27/87 Submission of Preclinical Information Amendment.

03/03/87 Letter requesting assistance in protocol.

03/26/87 Phone call to FDA to inquire into a zolpidem End-of-Phase II conference.

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CHRONOLOGY

04/01/87 Phone call to FDA to inquire into the status of Lorex's request for an End-of-Phase II conference for zolpidem.

04/10/87 Submission of Safety Report.

04/13/87 Phone call from FDA regarding zolpidem studies enrollment.

04/16/87 Submission of Safety Report.

04/20/87 Submission of Clinical Amendment.

04/30/87 Phone call to FDA to determine the status of letter requested.

05/01/87 Submission of Information Amendment.

05/15/87 Submission of new protocol; new Clinical Monitor for zolpidem; and Preliminary Report.

05/26/87 Submission of Information Amendment.

05/29/87 Submission of follow-up information to Safety Report.

06/01/87 Submission of follow-up information to Safety Report.

06/11/87 Letter from FDA regarding inclusion in zolpidem studies.

06/15/87 Submission of new investigator for protocol.

06/19/87 Submission of Protocol Amendment.

07/28/87 Response to FDA letter of 06/11/87 regarding inclusion in zolpidem studies.

07/31/87 Submission of new investigators for protocol and new subinvestigators for protocol study sites.

08/04/87 Phone call to FDA regarding the procedures regarding testing programs.

08/31/87 Submission of Protocol Amendment.

09/25/87 Submission of Preclinical Information Amendment.

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CHRONOLOGY

09/30/87 Submission of Protocol Amendments and new subinvestigators.

10/09/87 Letter to FDA requesting an End-of-Phase II meeting.

10/12/87 Submission of Information Amendment: Clinical and Summary.

10/15/87 Submission of new protocols.

10/22/87 Phone call to FDA (M. Mille) in follow-up to Lorex's 10/09/87 request for an End-of-Phase II meeting.

10/29/87 Submission of End-of-Phase II data package.

10/30/87 Submission of Protocol Amendment.

11/10/87 Phone call to FDA regarding End-of-Phase II meeting request.

11/18/87 Phone call to FDA regarding the prospect of an electronic NDA and End-of-Phase II meeting.

11/20/87 Phone call to FDA regarding the viability of an electronic NDA for zolpidem and the End-of-Phase II meeting.

11/24/87 Submission of new protocols and new investigators.

12/23/87 Submission of Annual Progress Report.

12/24/87 Submission of new subinvestigators for study sites.

1988

01/13/88 Phone call to FDA regarding status of Lorex's request for End-of-Phase II meeting.

01/14/88 Phone call to FDA with general questions regarding NDA submissions.

01/22/88 Submission of Information Amendment; Clinical - Summary Reports.

01/25/88 Submission of Safety Report.

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CHRONOLOGY

01/26/88 Phone call to FDA regarding status of FDA meeting request and an electronic NDA (ENDA).

01/27/88 Meeting with FDA regarding ENDAs and status of FDA meeting request.

01/28/88 Phone call to FDA in follow-up to meeting on 01/27/88.

Submission of protocol Amendment.

02/05/88 Phone call to FDA regarding status of our request for End-of-Phase II meeting.

02/12/88 Phone call to FDA regarding status of our request for End-of-Phase II meeting.

03/03/88 Phone call to FDA regarding status of our request for End-of-Phase II meeting.

Submission of new protocol Amendment.

03/15/88 Submission of follow-up Safety Report.

Phone call to FDA regarding status of our request for End-of-Phase II meeting.

03/16/88 Phone call from FDA notifying Lorex that FDA could meet with them on March 22, 1988.

03/22/88 End-of-Phase II Meeting with FDA.

03/31/88 Submission of new subinvestigators for study site.

04/08/88 Submission of Preclinical Information Amendment; toxicology reports.

04/12/88 Submission of new protocol LSH16 with Amendment.

05/31/88 Submission of Protocol Amendments.

06/08/88 Submission of Safety Report.

06/30/88 Submission of new subinvestigators study site.

07/28/88 Submission of new investigator for.

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CHRONOLOGY

08/16/88 Submission of Annual Progress Report.

08/30/88 Submission of new protocol and new subinvestigators for study site.

09/15/88 Phone call to FDA regarding reporting.

10/28/88 Submission of new subinvestigators study site.

Submission of Safety Report.

Letter from FDA requesting that Lorex submit data for study on computer-readable tape.

11/01/88 Submission of Safety Report.

11/07/88 Submission of Safety Report.

11/30/88 Submission of new subinvestigators for study site.

12/21/88 Phone call to FDA to discuss information, zolpidem update and European reports.

12/28/88 Submission of follow-up information to Safety Report.

1989

01/05/89 Phone call to FDA with questions regarding the computer tape requested by FDA on 10/28/88.

01/12/89 Phone call from FDA requesting that Lorex call Biometrics to discuss study.

01/13/89 Phone call to FDA regarding the data a report and the need to receive the computer tape.

01/25/89 Letter from FDA with requests and comments on studies.

02/01/89 Letter from FDA forwarding copies of FDA's minutes of the 3/22/88 End-of-Phase II meeting.

02/23/89 Submission of Safety Report.

02/24/89 Submission of Safety Report.

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CHRONOLOGY

02/28/89 Submission of a new subinvestigator for study site.

03/02/89 Phone call from FDA inquiring into the status of computer data tape for study.

04/05/89 Submission of follow-up information on Safety Report.

05/05/89 Submission of follow-up information on Safety Report.

04/17/89 Submission of new protocol.

04/21/89 Phone call to FDA regarding reports.

04/26/89 Meeting at FDA regarding the computer data tape for study.

04/27/89 Submission of Protocol Amendment.

05/05/89 Submission of three Amendments submitted to the zolpidem ND.

06/01/89 Submission of Protocol Amendment.

06/06/89 Submission of Safety Report.

06/26/89 Submission of curriculum vitae for replacement clinical monitor.

07/20/89 Submission of new protocol.

08/10/89 Submission of Safety Report.

09/06/89 Submission of new protocol.

09/14/89 Submission of new protocols with Amendments.

09/20/89 Submission of Annual Progress Report.

10/02/89 Submission of Protocol Amendment; new investigator for protocol and a new subinvestigator.

10/09/89 Submission of new protocols.

10/16/89 Submission of new protocol.

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CHRONOLOGY

10/31/89 Submission of new investigators for protocol and Protocol Amendment.

11/03/89 Submission of Safety Report.

11/08/89 Submission of Safety Report.

11/09/89 Submission of new protocol.

12/04/89 Submission of new investigators; new subinvestigator and Protocol Amendment.

12/04/89 Submission of new protocol.

12/07/89 Submission of new protocol.

12/22/89 Submission of new investigators for protocols.

1990

01/30/90 Submission of new investigator for protocol and new subinvestigators for sites.

02/02/90 Submission of a new protocol.

02/16/90 Submission of Safety Report.

02/26/90 Submission of new subinvestigator for study sites and new investigators for protocols.

03/02/90 Submission of new protocol with Amendments.

03/30/90 Submission of new subinvestigators and a study site change for study; new subinvestigator for study site; and a change in principal investigator.

04/27/90 Submission of a new subinvestigator for study site; new investigators for protocol; and protocol Amendments.

05/02/90 Submission of Safety Report.

05/09/90 Submission of Safety Report.

05/14/90 Submission of follow-up information to Safety Report.

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CHRONOLOGY

05/31/90 Submission of new investigator.

06/29/90 Submission of a new investigator for protocol.

07/27/90 Submission of new protocol.

07/30/90 Submission of a new investigator.

08/06/90 Submission of Safety Report.

09/04/90 Submission of Annual Progress Report.

09/06/90 Submission of new investigators and a new subinvestigator.

10/01/90 Phone call from FDA requesting that we send a desk copy of our July 27, 1990 IND submission of protocol.

10/02/90 Submission of new investigators.

Submission of Desk Copy of IND Submission as requested by FDA on 10/01/90.

11/07/90 Submission of new investigator and a new subinvestigator.

11/27/90 Submission of Safety Report.

12/05/90 Submission of Safety Report.

1991

01/08/91 Submission of new protocol.

01/31/91 Submission of new protocol.

02/19/91 Submission of Safety Report.

04/26/91 Submission of Safety Report.

07/11/91 Submission of Safety Report.

08/02/91 Submission of Safety Report.

08/15/91 Submission of Annual Progress Report.

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CHRONOLOGY

10/22/91 Submission of Safety Report.

12/05/91 Submission of new subinvestigators and Protocol Amendments.

ZOLPIDEM NDA CHRONOLOGY

1989

01/26/89 Original New Drug Application filed.

02/21/89 Letter from FDA acknowledging receipt of NDA (1/30/89) and projected filing date of 3/31/89.

03/10/89 Letter to Division of Biometrics with proposed naming conventions for the zolpidem CANADA.

03/13/89 Phone call from FDA informing Lorex that FDA was refusing to file the zolpidem NDA because they could not find the environmental impact analysis report, the a compliance statement, and details of a statistical evaluation study and other items requested previously under the IND.

Submitted rat computer data tape (other statements were in original NDA).

03/13-
03/15/89 Several phone calls to resolve issues around FDA's refusal to file zolpidem NDA including Chemist's inability to locate certificates of analysis.

03/16/89 Submission of U.S. clinical studies certificates of analysis.

03/20/89 Phone call from FDA inquiring about the status of study.

03/31/89 Submission of package with certificates of analysis in response to 3/15/89 discussion [documents were with individual study reports in original NDA].

04/04/89 Submission of documentation and hardware for CANADA.

04/18/89 Call from FDA requesting hard copy content listing of a tape and inquiring as to status of other outstanding items under the IND.

04/25/89 Phone call to clarify the tape format for the data; return call requesting data on floppy disk.

04/26/89 Visit regarding tape and impact on NDA review.

04/28/89 Submission of computer diskette with data.

05/04/89 Submission of Lorex statistical analyses and data used in a study.

ZOLPIDEM NDA CHRONOLOGY

05/19/89 Phone call to FDA to verify filing date of 3/31/89 and postponement of Four-Month Safety Update.

07/26-
07/27/89 Phone calls from FDA regarding study analysis.

08/01/89 Phone call to FDA with information requested on 7/27/89.

08/03/89 Phone call to FDA regarding status of NDA review.

08/31/89 Phone call from FDA notifying Lorex that they are ready to schedule inspections and requesting list of "principal" studies.

09/01/89 Phone call to FDA regarding status of review of a study.

09/07/89 Call from FDA requesting deck copy of information [original desk copies lost during move of Staff].

09/07-
09/13/89 Several calls with FDA regarding Lorex CANADA submission and requesting study data on diskette.

09/11/89 Submission of requested desk copy of information.

09/13/89 Submission of data on diskette.

Submission of information on "principal" studies to FDA.

Letter from FDA with comments and requests regarding chemistry, manufacturing and controls.

09/25/89 Phone call from FDA requesting selected case report forms.

10/19/89 Submission of case report forms as requested on 9/25/89.

11/07/89 Phone call to FDA regarding status of NDA review.

1990

01/02/90 Call from FDA with questions regarding the change in synthesis of zolpidem and which preclinical studies were conducted with old and new routes, respectively.

ZOLPIDEM NDA CHRONOLOGY

01/05/90 Phone call to FDA with information regarding studies conducted with the two drug substance routes and references to NDA pages on which listings could be found.

02/02/90 Call from FDA requesting two more desk copies of information submitted on 9/11/89.

02/07/90 Additional desk copies sent.

02/12/90 Submission of clinical report for evaluation study.

02/16/90 Phone call from FDA requesting letter of authorization to release data.

02/19/90 Submission of authorization letter allowing FDA to release data to NIDA.

03/21/90 Phone call to FDA regarding status of NDA review.

03/22/90 Submission of data.

03/27/90 Visit with FDA Staff to introduce them to Lorex and determine their procedures for communications and reviews.

04/03/90 Phone call from FDA to determine whether they were missing a (11/08/90) submission to Lorex's NDA.

04/06/90 Phone call from FDA with questions regarding data analysis and requesting a new copy of the datasets.

04/19/90 Submission of response to FDA requests.

04/25/90 Submission of seven diskettes with background materials.

05/01/90 FDA acknowledgment of 4/19/90 submission and notification that an additional 60 days will be needed for review.

05/03/90 Phone call to FDA requesting a meeting with him to discuss Lorex's response to comments Lorex received.

05/25/90 Phone call from FDA concerning questions he was encountering.

05/29/90 Phone call from FDA regarding rationale for the data analysis.

06/01/90 Several phone calls from FDA with questions regarding the use of datasets.

ZOLPIDEM NDA CHRONOLOGY

08/02/90 Phone call to FDA regarding status of NDA.

08/08/90 Letter to FDA requesting a meeting with Staff.

08/15/90 Letter from FDA with comments.

08/27/90 Phone call from FDA concerning guidelines for non-physicians who were named as principal investigators for a clinical study.

08/28/90 Phone call from FDA regarding the registration status of zolpidem and the location of the worldwide literature on zolpidem in the NDA.

08/29/90 Follow-up phone call to FDA regarding guidelines.

09/24/90 Phone call to FDA regarding our 8/8/90 meeting request.

10/01/90 Phone call from FDA requesting a desk copy of protocol.

10/02/90 Submission of requested desk copy of protocol.

10/03/90 Meeting with FDA to discuss status of zolpidem NDA.

11/07/90 Meeting between Lorex, Searle and FDA to discuss preparation of Environmental Assessment Report.

12/17/90 Submission of Lorex minutes of 11/07/90 meeting to FDA.

1991

01/07/91 Submission of Lorex SOP 311 in response to FDA request.

01/16/91 Phone call from FDA requesting 1) additional information 2) a dose proportionality analysis and 3) clarification on the dosage strengths Lorex intends to market.

Phone call from FDA with questions pertaining to a Summary.

01/17/91 Phone call to FDA in response to his request of 01/16/91 for clarification.

Phone call from FDA with questions pertaining to study report.

01/22/91 Phone call to FDA regarding status of zolpidem NDA.

ZOLPIDEM NDA CHRONOLOGY

01/23/91 Phone call from FDA inquiring into the status of final study reports.

01/28/91 Phone call to FDA concerning zolpidem scheduling.

Phone call from FDA with additional requests concerning analysis of zolpidem.

02/04/91 Submission of revised tables to a Summary as requested by Dr. D. Collins on 01/16/91.

Submission of supplementary analysis of the study as requested by Dr. D. Gordin on 01/16/91.

Submission of final study reports as requested by Dr. T. Laughren on 01/23/91.

02/05/91 Phone call from FDA requesting that Lorex prepare a Summary Basis of Approval for zolpidem.

02/06/91 Phone call to FDA regarding scheduling of zolpidem.

Conference call between Lorex and FDA in response to a series of requests (01/28/91) concerning zolpidem.

02/07/91 Letter from FDA providing Lorex with a copy of Staff's final review of a study.

02/08/91 Letter from FDA acknowledging receipt of the two amendments dated 02/04/91.

Phone call to Dr. Sheu of a National Institute regarding the scheduling of zolpidem.

02/11/91 Letter from FDA supplying Lorex with a copy of a draft document.

02/18/91 Submission of case report forms.

02/20/91 Submission of listings to facilitate review of case report forms submitted on 02/18/91.

02/25/91 Phone call from DA requesting randomization codes.

02/26/91 Submission of case report forms as requested on 02/06/91.

03/01/91 Meeting between Lorex and FDA to resolve zolpidem issues.

ZOLPIDEM NDA CHRONOLOGY

03/04/91 Phone call from FDA in follow-up to 3/01/91 meeting.

Conference call between FDA and Lorex to clarify information.

03/05/91 Phone call from FDA requesting information on specific studies conducted.

03/06/91 Phone call from FDA requesting information.

Submission of additional data as requested by Dr. D. Collins on 02/06/91.

03/07/91 Submission of additional information as originally requested on 02/06/91.

Phone call from FDA requesting additional information on studies in hardcopy and on diskette.

Telefax from FDA which outlines the desired format to be used when supplying data requested for studies.

03/08/91 Submission of table as requested by Dr. Collins on 03/05/91.

03/12/91 Phone call from FDA inquiring into status.

Phone call from FDA requesting information on studies.

03/13/91 Phone call to FDA in follow-up to 03/12/91 phone call requesting information.

03/15/91 Submission of two reformatted data tables from study report as requested on 03/07/91.

03/27/91 Phone call from FDA requesting demographic tables from studies.

04/01/91 Submission of
1) Environmental Assessment Report (requested on 11/09/91),
2) Update (discussed at 03/01/81 meeting), and
3) additional information as requested in an 08/15/90 letter from FDA

Submission of study synopses for study reports (in hard copy and on diskette) as requested on 03/07/91.

ZOLPIDEM NDA CHRONOLOGY

04/03/91 Phone call from FDA requesting information and was given the volume and page reference where it was located in the NDA.

04/08/91 Phone call from FDA requesting a description of tablet formulations.

04/15/91 Letter from FDA acknowledging receipt of Lorex's April 1, 1991 submission.

04/17/91 Response to request of 04/08/91 for a description of tablet formulations.

04/29/91 Phone call to FDA inquiring into status of his review of the data.

05/03/91 Phone call to FDA inquiring into status of zolpidem NDA review.

05/10/91 Phone call from FDA inquiring into status of FDA request for additional data.

05/15/91 Phone call from FDA requesting information.

05/23/91 Submitted additional data in response to request of 03/12/91.

06/03/91 Phone call to FDA regarding status of zolpidem analysis.

Phone call to FDA in follow-up to request of 5/5/91 for information.

06/04/91 Phone call to FDA regarding status of review.

06/06/91 Phone call from FDA regarding an inspection of the zolpidem manufacturing facilities.

06/17/91 Phone call from FDA seeking clarification of Lorex's 2/26/91 submission.

06/18/91 Phone call to FDA regarding status of zolpidem review.

Phone call to FDA inquiring into the status of his review of the zolpidem environment assessment report.

06/19/91 Phone call to FDA regarding status of zolpidem review.

ZOLPIDEM NDA CHRONOLOGY

06/20/91 Written confirmation that Lorex's statistical analysis for all principal clinical efficacy trials were conducted utilizing two-sided tests.

06/26/91 Response to request of 06/04/91 for information.

06/28/91 Submission of Final Study Report, Draft Summary Basis of Approval, CMC Response, European Post-Marketing Safety Data.

Phone call from FDA requesting additional information.

07/01/91 Phone call from FDA inquiring into status of Draft Summary Basis of Approval.

07/01-
07/02/91 Visits made to several zolpidem NDA reviewers to discuss status of zolpidem NDA.

07/12/91 Conference call between FDA and Lorex to discuss the purpose of protocol.

07/15/91 Phone call from FDA requesting information.

07/16/91 Submission of previously telefaxed information.

07/18/91 Follow-up phone call to request of 6/28/91 on reports.

Phone call to FDA concerning zolpidem draft summary basis of approval.

07/19/91 Phone call to FDA regarding status of pre-approval site inspections.

07/24/91 Response to request of 6/28/91.

07/26/91 Phone call to FDA regarding status of chemistry review.

08/01/91 Phone call to FDA regarding request for clarification of issues.

08/01/91 Phone call to FDA regarding the status of the chemistry review and schedule for pre-approval inspections.

08/02/91 Response to request for clarification of issues.

08/05/91 Phone call from FDA regarding a request for additional chemistry information and the status of the zolpidem review.

ZOLPIDEM NDA CHRONOLOGY

08/05/91 Phone call from FDA requesting the location and address for the zolpidem drug substance and drug product manufacturing facilities.

08/07/91 Response to 08/05/91 request for zolpidem drug substance and drug product manufacturing site locations.

Letter from FDA acknowledging receipt of June 28, 1991 amendment.

08/14/91 Response to issues raised in FDA correspondence dated 2/7/91.

08/15/91 Phone call from FDA regarding CMC issues and the status of the chemistry review.

08/15/91 Phone call to FDA regarding the status of the zolpidem review.

08/19/91 Phone call to DA regarding the adequacy of the tartrate vs. hemitartrate supplement response.

08/20/91 Phone call from FDA requesting a meeting to discuss the outstanding zolpidem chemistry issues.

08/21/91 Phone call from FDA to set a meeting date to discuss outstanding chemistry issues.

08/26/91 Response to issues raised by FDA.

08/28/91 Meeting with FDA regarding outstanding zolpidem chemistry issues.

08/29/91 Meeting with FDA regarding the current status of the zolpidem NDA.

09/06/91 Submitted copy of 8/28/91 Lorex/FDA CMC meeting minutes to FDA.

09/09/91 Phone call from FDA to discuss the pre-approval inspection of Searle/Caguas and Synthelabo's long-term stability data.

Phone call to FDA regarding observations made by FDA investigator during inspection of Searle/Caguas.

09/10/91 Phone call to FDA to inquiring into what could be done to expedite completion of the chemistry review.

ZOLPIDEM NDA CHRONOLOGY

10/01/91 Phone call to FDA to inquire into whether a scheduled time had been set for FDA to inspect the Synthelabo Porchville and Mourenx facilities.

Phone calls to FDA San Juan District Office to confirm their receipt of Lorex's response to the Form 483 and to inquire into the review process.

Phone call to FDA regarding the status of the chemistry review and Form 483 response.

10/02/91 Phone call to FDA to discuss decision regarding a Schedule IV or V assessment for zolpidem.

Phone call from FDA to discuss the zolpidem labeling.

10/04/91 Teleconference call with FDA to discuss data and labeling.

10/09/91 Phone call to FDA regarding the status of the zolpidem chemistry review and to determine if Lorex's 483 response had been reviewed.

10/15/91 Response to issues raised in a 10/04/91 teleconference with Lorex regarding zolpidem data and labeling.

Phone call to FDA regarding the scheduling of the French manufacturing facilities inspections.

10/16/91 Phone call to FDA regarding the status of the zolpidem NDA review.

10/28/91 Phone call to FDA to follow-up on the foreign inspection scheduling.

10/29/91 Phone call to FDA regarding documentation required to finalize the French facilities inspections.

11/21/91 Phone call from FDA inquiring into whether the proposed 10mg product would be scored and updating Lorex on the status of the zolpidem NDA review.

12/04/91 Phone call to FDA regarding the status of the zolpidem NDA review.

12/12/91 Several phone calls to FDA regarding the status of the zolpidem review.

Phone call from FDA to inform Lorex that he was close to completion of his review of the zolpidem NDA; the action package would be sent for signoff; and approximately one month from now Lorex would receive the approvable letter with labeling and patient package insert.

12/13/91 Letter to FDA requesting meeting.

12/10/91 Letter to FDA regarding zolpidem clinical investigator.

Letter to FDA regarding zolpidem clinical investigator.

1992

01/13/92 Phone call to FDA regarding the status of the zolpidem NDA review and the upcoming Advisory Committee meeting for zolpidem scheduling.

01/16/92 Phone call to FDA to inquire into whether validation samples could be picked up by FDA inspectors who were at the Searle Puerto Rico facility.

01/29/92 Letter of authorization permitting representatives from NIDA to have access to all documents pertaining to the zolpidem NDA submission.

01/30/92 Minutes of a Lorex/FDA (Pilot Drug Division) meeting, to discuss the zolpidem presentation for scheduling assessment at the upcoming Drug Advisory Committee meeting.

02/03/92 Zolpidem package sent to FDA.

02/04/92 Submission of post-marketing report and three preprinted articles from Synthelabo investigators.

02/18/92 Submission of supplementary document.

02/20/92 Phone call to FDA regarding the status of the zolpidem review.

02/20/92 Telefax regarding NIDA's review of zolpidem.

03/03/92 Phone call with a question regarding a previous zolpidem CMC filing and notifying Lorex that the zolpidem approval package will be moved up to Dr. Temple's office by 03/05/92.

ZOLPIDEM NDA CHRONOLOGY

03/11/92 Phone call to FDA regarding status of zolpidem scheduling.

03/13/92 Phone call from FDA informing Lorex that zolpidem passed recent inspection at the Searle Caguas facility and that it should receive a 24 month shelf-life dating.

03/18/92 Phone call to NIDA on status of zolpidem scheduling.

03/19/92 Phone call from FDA requesting that we provide a letter of cross-reference.

Phone call to FDA on status of zolpidem scheduling which will move to the office of the Assistant Secretary of Health within the next two days.

03/24/92 Phone call from FDA regarding the status of the approvable letter for zolpidem.

04/02/92 Phone call to FDA to determine whether they had received the individual written positions from NIDA and FDA on zolpidem scheduling.

04/09/92 Phone call to FDA regarding status of Approvable Letter.

04/14/92 Phone call to FDA regarding status of Approvable Letter.

04/17/92 Phone call to FDA regarding status of zolpidem scheduling.

04/21/92 Phone call from FDA regarding the status of the Approvable Letter.

APPROVABLE LETTER from FDA on zolpidem NDA.

04/22/92 Letter to FDA acknowledging receipt of Approvable Letter.

05/22/92 Phone call to FDA regarding status of zolpidem scheduling.

Phone call to FDA to schedule the labeling meeting on zolpidem with FDA.

06/08/92 Phone call to FDA regarding status of zolpidem scheduling.

07/02/92 Phone call to FDA regarding zolpidem labeling and advertising issues.

ZOLPIDEM NDA CHRONOLOGY

07/30/92 Response to approvable letter.

08/07/92 Phone call to NIDA regarding results of the joint FDA/NIDA meeting to resolve the scheduling issues on zolpidem.

08/10/92 Phone call to FDA regarding results of the joint FDA/NIDA meeting to resolve the scheduling issues on zolpidem.

08/11/92 Phone call to FDA regarding results of the joint FDA/NIDA meeting to resolve the scheduling issues on zolpidem.

Phone call from FDA requesting desk copies of Volume 1 of Lorex's response to the approvable letter.

Submission of above requested desk copies to FDA.

08/12/92 Phone call to FDA regarding zolpidem tablet markings.

08/18/92 Acknowledgment letter from FDA of Lorex's 7/30/92 submission.

09/01/92 Phone call to FDA regarding the status of the review of Lorex's response to the FDA approvable letter for zolpidem.

09/16/92 Phone call from FDA requesting two additional desk copies of part of Lorex's response to the zolpidem approvable letter.

Submission of above requested desk copies to FDA.

09/17/92 Response to FDA request for an additional analysis.

09/23/92 Phone call to FDA concerning the status of the review of Lorex's response to the FDA approvable letter for zolpidem.

09/29/92 Phone call to FDA concerning the status of the review of our response to the FDA approvable letter for zolpidem and whether a date had been set to discuss labeling issues.

10/02/92 Phone call to DEA regarding the scheduling notice for Ambien in the Federal Register.

ZOLPIDEM NDA CHRONOLOGY

10/09/92 Phone call from FDA regarding the status of the Ambien within FDA, labeling and requesting that Lorex withdraw three efficacy studies.

10/14/92 Phone call to FDA to inform FDA that Lorex would not include the three efficacy studies as part of Lorex labeling discussions.

Phone call from FDA to set a tentative labeling meeting date for November 9th.

10/19/92 Submission of copies of the labeling and a desk copy of a Volume of the response to the approvable letter as requested on 10/14/92.

10/21/92 Submission of Revised Safety Update.

10/27/92 Phone call from FDA requesting clarification of certain issues within the Revised Safety Update.

Submission of labeling on diskette as requested.

10/30/92 Phone call to FDA concerning what issues would be discussed at the meeting.

11/04/92 Memorandum from FDA requesting additional information.

Received telefax from Dr. Laughren of the Draft Final Labeling Proposal for 11/9/92 Meeting with FDA.

11/06/92 Memorandum from FDA requesting additional information.

11/06/92 Submission of additional stability data and a request for a meeting with FDA to discuss this issue.

11/06/92 Memorandum to FDA with a proposed agenda for the 11/09/92 meeting.

11/16/92 Submission of a line listing regarding U.S. patients.

Submission of reanalysis of the efficacy parameters from a study.

11/17/92 Submission of line listings.

Phone call to DEA regarding Federal Register announcement concerning the Ambien scheduling.

ZOLPIDEM NDA CHRONOLOGY

11/18/92 Phone call from FDA regarding extension of expiration dating for Ambien.

11/19/92 Submission of narrative descriptions.

Conference call with FDA regarding reanalysis of a protocol.

11/23/92 Submission of additional statistical analysis as requested by FDA on 11/19/92.

11/30/92 Telefax with labeling as discussed at the 11/09/92 meeting.

12/04/92 Submission of line listings and narratives.

Submission of revised draft labeling.

12/08/92 Phone call from FDA requesting Environmental Assessment Report to be resubmitted with specific segments marked "Confidential Business Information".

Environmental Assessment Report resubmitted as requested.

12/15/92 Phone call from FDA regarding Environmental Assessment Report submitted 12/8/92.

12/16/92 **APPROVAL LETTER** received from FDA.

12. STATEMENT CONCERNING LENGTH OF EXTENSION

It is believed that U.S. Patent No. 4,382,938 is eligible for an extension of five years. The length of extension is determined as follows:

IND 25,361 was pending from November 15, 1984 through January 26, 1989, a total of 1534 days. For purposes of calculating the extension, this is reduced by 1/2, i.e., to 767 days. NDA 19,908 was pending from January 26, 1989 through December 16, 1992, a total of 1421 days. Therefore, the total extension from the IND period and the NDA period is 2188 days. This corresponds to, including 1 leap year, 5 years, 362 days.

Since no request for exemption was submitted before September 24, 1984, pursuant to 37 CFR 1.775(c)(6)(i) the maximum extension is five years. Adding 5 years to the original expiration date of the patent is earlier than 14 years later than the approval date. Therefore, the maximum extension available is five years.

13. DUTY OF DISCLOSURE

Applicant hereby acknowledges the duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

14. FEE

A check in the amount of $1,000.00 accompanies this application. Any deficiency may be charged to Deposit Account No. 23-0783.

15. CORRESPONDENCE ADDRESS

Correspondence relating to this application for patent term extension should be directed to:

Douglas P. Mueller, Esq.
WEGNER, CANTOR, MUELLER & PLAYER
P. O. Box 18218
Washington, DC 20036-8218
(202) 887-0400

16. DUPLICATE OF THE APPLICATION PAPERS

Filed herewith is a certified duplicate of the application papers.

17. DECLARATION

The undersigned declares that:

1. He is an official of the corporate owner of U.S. Patent No. 4,382,938, authorized to obligate the corporation;

2. He has reviewed and understands the contents of the application for extension of the term of U.S. Patent No. 4,382,938;

3. He believes the patent is subject to extension in accordance with 37 CFR 1.710;

4. He believes an extension of five years is justified under 35 USC 156 and the applicable regulations; and

5. He believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 CFR 1.720.

He further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

19 January 1993
DATE

Typed Name: Regis DUFOUR
Title: Executive Vice-President

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ROUTE ORIG.
COPY TO
FOLLOW UP

NDA 19-908

DEC 16 1992

Lorex Pharmaceuticals
Attention: Keith Rotenberg, Ph.D.
P.O. Box 163
4930 Oakton Street
Skokie, Illinois 60077

Dear Dr. Rotenberg:

Reference is made to your new drug application dated January 26, 1989, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for AMBIEN (zolpidem tartrate) tablets, NDA 19-908.

We also acknowledge receipt of and/or refer to your additional communications dated:

September 17, 1992	November 16, 1992 (2 submissions)
October 19, 1992	November 17, 1992
October 21, 1992	November 19, 1992
October 27, 1992	November 23, 1992
November 4, 1992	December 4, 1992 (2 submissions)
November 6, 1992	

We have completed our review of this application, as amended, including the submitted draft labeling and patient package insert (PPI), and we have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final draft of labeling that accompanies this letter (as Attachment 1). Accordingly, the application, with the enclosed draft labeling, is approved, effective as of the date of this letter.

Labeling/PPI

Regarding labeling and the PPI, we refer to our meeting with you on 11-9-92 to discuss labeling and a PPI for Ambien. At this meeting, we focused on FDA's 11-4-92 drafts (faxed to you in preparation for this meeting) of these documents. We reached substantial but not complete agreement at this meeting. On 11-30-92, Dr. Laughren faxed you another version of these documents that incorporated all of the agreed upon changes and also contained proposals for those few remaining sections upon which we had not yet reached agreement. You responded with a 12-4-92 fax containing your counter-proposals for these documents. We found many of the additional revisions to be minor and acceptable, and we have incorporated these changes into the final drafts of these documents that accompany this letter. However, there remain 2 primary areas of disagreement: Indications and Usage, and Contraindications. You prefer an Indications and Usage section that does not include a

recommendation to re-evaluate patients needing therapy beyond 2-3 weeks and does not limit prescriptions to 1 month. Since we are in the process of trying to implement such changes for all hypnotics, we feel it is both fair and essential to obtain this language for Ambien at this stage. You also want to contraindicate Ambien during pregnancy, primarily for liability reasons. However, we do not believe there is a sufficient basis for such a contraindication. Consequently, the drafts of labeling and PPI that accompany this letter contain language in these sections not previously agreed to by you. In addition, there were some minor modifications proposed in your 12-4-92 draft that we did not consider acceptable and these have not been incorporated. We have also made some minor modifications not previously agreed to, none of which we expect to be controversial. The drafts of labeling and PPI contain bracketed comments that refer to which proposed modifications (12-4-92) were accepted, and which were not, and also refer to any additional minor modifications.

Several other labeling/PPI issues need comment:

-In a cover letter for the 12-4-92 fax, you asked that FDA reconsider a much shorter form of the PPI, despite the fact that we had reached agreement with you on 11-9-92 about a longer form. Given that we are attempting to implement a longer form for all hypnotics, we feel that it is both fair and essential that we persist in our requirement for the longer form of the PPI for Ambien.

-In our 11-9-92 meeting with you, we had asked you to prepare a 'Geriatric Use' subsection under Precautions, addressing the size of the elderly population studied in your development program and brief comments on what was found regarding safety. In the 12-4-92 fax, you indicated that you do not plan to add such a subsection. We continue to feel that such a subsection would be useful, and we ask that you prepare such a statement for inclusion in labeling after approval.

The final printed labeling (FPL) must be identical to the draft labeling/PPI under Attachment 1. Marketing the product with FPL that is not identical to the draft labeling under Attachment 1 may render the product misbranded and an unapproved new drug.

Please submit twelve copies of the FPL to FDA as soon as available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 19-908." Approval of this supplement by FDA is not required before the labeling may be used. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

Unit-of-use Packaging

While we acknowledge your arguments against the implementation of unit-of-use packaging for Ambien, we still intend to pursue such packaging since we consider it to be in the public interest. Nevertheless, we do not feel that the approval of this NDA should be held up on this basis. Consequently, we do not object to your plans for alternative packaging for Ambien at the present time.

Please submit one market package of the drug product when it is available.

Expiration Dating

On March 13, 1992, you were informed by Dr. Stanley Blum of this Division that your stability data supported a two (2) year expiration date for the 5 and 10 mg tablets. However, in a November 6, 1992 submission, you requested an extension of the expiration date from two (2) years to three (3) years. We have concluded that the available data do not support an extension of the expiration date to three (3) years.

The expiration date may be extended pursuant to 21 CFR 314.70(d)(5). The full shelf-life data (e.g., 3 years) obtained according to the stability protocol approved as part of the application must be submitted, and the expiration date change described, in an annual report.

Methods Validation

The validation of the analytical methods has not been completed for this application. We will expect your full cooperation in resolving any problems that may arise.

Advertising Copy

Please submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Neuropharmacological Drug Products, and the second copy to the Division of Drug Marketing, Advertising and Communications, HFD-240, Room 11B-06, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Should questions arise concerning this NDA, please contact Mr. Merril Mille, Regulatory Management Officer, at (301) 443-3830.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT 1

FINAL LABELING PROPOSAL

Ambien
(Zolpidem Tartrate Tablets)

[When the scheduling of Ambien is finalized, please insert classification symbol in the top right hand corner of the labeling.]

DESCRIPTION

Ambien (zolpidem tartrate), is a non-benzodiazepine hypnotic of the imidazopyridine class and is available in 5 mg and 10 mg strength tablets for oral administration.

Chemically, zolpidem is N,N,6-trimethyl-2-p-tolyl-imidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:

[Insert structure here.]

Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.

Each Ambien tablet includes the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, titanium dioxide, FD&C Red No. 40 (5 mg strength only).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Subunit modulation of the $GABA_A$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic and myorelaxant drug properties. The major modulatory site of the $GABA_A$ receptor complex is located on its α (alpha) subunit and is referred to as the benzodiazepine (BZ) or omega (ω) receptor. At least three subtypes of the (ω) receptor have been identified.

While zolpidem is an hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates or other drugs with known hypnotic properties, it interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-

selectively bind to and activate all three omega receptor subtypes, zolpidem in vitro binds the (ω_1) receptor preferentially. The (ω_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus and globus pallidus. This selective binding of zolpidem on the (ω_1) receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stage 3-4) in human studies of zolpidem at hypnotic doses.

Pharmacokinetics

The pharmacokinetic profile of AMBIEN is characterized by rapid absorption from the GI tract and a short elimination half-life ($T_{\frac{1}{2}}$) in healthy subjects. In a single dose crossover study in 45 healthy subjects administered 5 and 10 mg zolpidem tartrate tablets, the mean peak concentrations (C_{max}) were 59 (range 29-113) and 121 (range 58-272) ng/ml, respectively, occurring at a mean time (t_{max}) of 1.6 hours for both. The mean AMBIEN elimination half-life was 2.6 (range: 1.4-4.5) and 2.5 (1.4-3.8) hours, for the 5 and 10 mg tablets, respectively. AMBIEN is converted to inactive metabolites that are eliminated primarily by renal excretion. AMBIEN demonstrated linear kinetics in the dose range of 5 to 20 mg. Total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/ml. Zolpidem did not accumulate in young adults following nightly dosing with 20 mg zolpidem tartrate tablets for 2 weeks.

A food effect study in 30 healthy male volunteers compared the pharmacokinetics of AMBIEN 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food mean AUC and C_{max} were decreased by 15% and 25%, respectively, while mean T_{max} was prolonged by 60% (from 1.4 to 2.2 hours). The half-life remained unchanged. These results suggest that, for faster sleep onset, AMBIEN should not be administered with or immediately after a meal.

In the elderly, the dose for AMBIEN should be 5 mg (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). This recommendation is based on several studies in which the mean C_{max}, $T_{\frac{1}{2}}$ and AUC were significantly increased when compared to results in young adults. In one study of 8 elderly subjects (>70 years), the means for C_{max}, $T_{\frac{1}{2}}$ and AUC significantly increased by 50% (255 vs 384 ng/ml), 32% (2.2 vs 2.9 hr) and 64% (955 vs 1,562 ng·hr/ml), respectively, as compared to younger adults (20-40 yrs) following a single 20 mg oral zolpidem dose. AMBIEN did not accumulate in elderly subjects following nightly oral dosing of 10 mg for one week.

The pharmacokinetics of AMBIEN in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects.

Following a single 20 mg oral zolpidem dose, mean C_{max} and AUC were found to be 2 times (250 vs 499 ng/ml) and 5 times (788 vs 4,203 ng·hr/ml) higher, respectively, in the hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 hrs (range: 4.1-25.8 hrs) was greater than that observed in normals of 2.2 hrs (range: 1.6-2.4 hrs). Dosing should be modified accordingly in patients with hepatic insufficiency. (see PRECAUTIONS and DOSAGE and ADMINISTRATION).

[Please note that the AUC units are expressed incorrectly in the following paragraph of your 12-4-92 draft.]

The pharmacokinetics of AMBIEN were studied in 11 patients with end stage renal failure (mean CrCl = 6.5 ± 1.5 ml/min) undergoing hemodialysis three times a week, who were dosed with zolpidem 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max}, T_{max}, half-life and AUC between the first and last day of drug administration when baseline concentrations adjustments were made. On day 1, C_{max} was 172 ± 29 ng/ml (range: 46-344 ng/ml). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/ml (range: 28-316 ng/ml). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5-3.0 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5-2.0 hr). This variation is accounted for by noting that last day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On day 1, $T_{\frac{1}{2}}$ was 2.4 ± 0.4 hrs (range: 0.4-5.1 hrs). After repeated dosing, $T_{\frac{1}{2}}$ was 2.5 ± 0.4 hrs (range: 0.7 - 4.2 hrs). AUC was 796 ± 159 ng·hr/ml after the first dose and 818 ± 170 ng·hr/ml after repeated dosing. Zolpidem was not hemodializable. No accumulation of unchanged drug appeared after 14 or 21 days. AMBIEN pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function. As a general precaution, these patients should be closely monitored.

Postulated Relationship Between Elimination Rate of Hypnotics and their Profile of Common Untoward Effects

[Please note that we have adopted the changes in the next to last sentence of the following paragraph, as suggested in your 12-4-92 draft. However, we have not added your final sentence on daytime anxiety; as discussed at our 11-9-92 meeting, we feel that the trials from which the referenced data were obtained lacked sensitivity, and thus, it would not be informative to report these negative findings.]

The type and duration of hypnotic effects and the profile of unwanted effects during administration of hypnotic drugs may be influenced by the biologic half-life of administered drug and any active metabolites formed. When half-lives are long, drug or metabolites may accumulate during periods of nightly administration

and be associated with impairments of cognitive and/or motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives, including half-lives of active metabolites, are short, drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to excessive sedation or CNS depression should be minimal or absent. Ambien has a short half-life and no active metabolites. During nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of hypnotics may develop. If the drug has a short elimination half-life, it is possible that a relative deficiency of the drug or its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of other rapidly eliminated hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety. Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with Ambien.

Controlled Trials Supporting Efficacy and Safety

Transient Insomnia

Normal adults experiencing transient insomnia (n=462) during the first night in a sleep laboratory were evaluated in a double-blind, parallel group, single-night trial comparing 2 doses of zolpidem (7.5 and 10 mg) and placebo. Both zolpidem doses were superior to placebo on objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings

Chronic Insomnia

[We have made several of the changes in this paragraph suggested in your 12-4-92 draft, however, we have not deleted information regarding the 15 mg dose. The experiment included a 15 mg group, and although 15 mg is not a recommended dose, the prescriber is entitled to know the full results of this study.]

Adult outpatients with chronic insomnia (n=75) were evaluated in a double-blind, parallel group, 5-week trial comparing 2 doses of zolpidem tartrate (10 and 15 mg) and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 15 mg was superior to placebo for all 5 weeks; zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied.

[We have made several of the changes in this paragraph

suggested in your 12-4-92 draft, however , we have not deleted information regarding the 15 mg dose, for the same reason noted above.]

Adult outpatients (n=141) with chronic insomnia were evaluated in a double-blind, parallel group, 4-week trial comparing 2 doses of zolpidem (10 and 15 mg) and placebo. Zolpidem 10 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep quality for the first week. Zolpidem 15 mg was superior to placebo on a subjective measure of sleep latency for the first 3 weeks, on a subjective measure of total sleep time for the first week, and on number of awakenings and sleep quality for the first 2 weeks.

Next Day Residual Effects

[We have accepted some, but not all, of your 12-4-92 proposed modifications for this paragraph.]

There was no evidence of residual next-day effects seen with Ambien in several studies utilizing the Multiple Sleep Latency Test (MSLT), the Digit Symbol Substitution Test (DSST), and patient ratings of alertness. In one study involving elderly patients, there was a small but statistically significant decrease in one measure of performance, the DSST, but no impairment was seen in the MSLT in this study.

Rebound Effects

[We have largely accepted your 12-4-92 proposed modification of this paragraph, however, we have also made a minor modification of our own.]

There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of AMBIEN. There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg.

Memory Impairment

[We have largely accepted your 12-4-92 proposed modification of this paragraph, however, we have also made minor modifications of our own.]

Two small studies (n=6 and n=9) utilizing objective measures of memory yielded little evidence for memory impairment following the administration of Ambien. There was subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of Ambien predominantly at doses above 10

mg.

Effects on Sleep Stages

In studies that measured the percentage of sleep time spent in each sleep stage, AMBIEN has generally been shown to preserve sleep stages. Sleep time spent in stage 3-4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

INDICATIONS AND USAGE

[We do not agree with the modifications proposed in your 12-4-92 draft, and we have left this section as written in our 11-30-92 draft.]

AMBIEN (zolpidem tartrate) is indicated for the short-term treatment of insomnia. Hypnotics should generally be limited to 7-10 days of use, and re-evaluation of the patient is recommended if they are to be taken for more than 2-3 weeks.

AMBIEN should not be prescribed in quantities exceeding a 1-month supply (see WARNINGS).

AMBIEN has been shown to decrease sleep latency and increase the duration of sleep for up to 5 weeks in controlled clinical studies (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

[We do not agree with the modifications proposed in your 12-4-92 draft. We continue to believe that there is not a sufficient basis to contraindicate Ambien in pregnancy. Consequently, we have left this section as written in our 11-30-92 draft.]

None known.

WARNINGS

[We have added the slight modification to the first paragraph of this section proposed in your 12-4-92 draft.]

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness which should be evaluated. Worsening of insomnia

or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including Ambien. Because some of the important adverse effects of AMBIEN appear to be dose related (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), it is important to use the smallest possible effective dose, especially in the elderly.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see DRUG ABUSE AND DEPENDENCE).

AMBIEN, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, AMBIEN should only be ingested immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of AMBIEN. AMBIEN showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when AMBIEN is administered with such agents because of the potentially additive effects.

PRECAUTIONS

General

Use in the Elderly and/or Debilitated Patients - Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended AMBIEN dosage is 5 mg in such patients (see DOSAGE AND ADMINISTRATION) to decrease the possibility of side effects. These patients should be closely monitored.

Use in Patients With Concomitant Illness - Clinical experience with AMBIEN in patients with concomitant systemic illness is limited. Caution is advisable in using AMBIEN in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although preliminary studies did not reveal respiratory depressant effects at hypnotic doses of AMBIEN in normals, precautions should be observed if AMBIEN is prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Data in end stage renal failure patients repeatedly treated with AMBIEN did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required, however, these patients should be closely monitored. (see PHARMACOKINETICS). A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored.

Use in Depression - As with other sedative/hypnotic drugs, AMBIEN should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Information for Patients

[We have made the modifications to this paragraph suggested in your 12-4-92 draft.]

Patient information is printed at the end of this insert. To assure safe and effective use of Ambien, this information and instructions provided in the patient information section should be discussed with patients.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

CNS Active Drugs - AMBIEN was evaluated in healthy volunteers in

single dose interaction studies for several CNS drugs. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. The lack of a drug interaction following single dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated.

Since the systematic evaluations of AMBIEN in combination with other CNS active drugs have been limited, careful consideration should be given to the pharmacology of any CNS active drugs to be used with zolpidem. Any drug with CNS depressant effects could potentially enhance the CNS depressant effects of zolpidem.

Other Drugs - A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil, however, no significant alterations in zolpidem pharmacokinetics were found.

Drug/Laboratory Test Interactions

Zolpidem is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Zolpidem was administered to rats and mice for two years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26-520 times or 2-35 times the maximum 10 mg human dose on a mg/kg or mg/m^2 basis, respectively. In rats these doses are 43-876 times or 6-115 times the maximum 10 mg human dose on a mg/kg or mg/m^2 basis, respectively. No evidence of carcinogenic potential was observed in mice. Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.

Mutagenesis: Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured human lymphocytes,

unscheduled DNA synthesis in rat hepatocytes in vitro, and the micronucleus test in mice.

Impairment of Fertility: In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4-100 mg base/mg or 5-130 times the recommended human doses in mg/m^2. No effects on any other fertilily parameters were noted.

Pregnancy:

[As discussed under Contraindications, we do not believe there is a sufficient basis to contraindicate Ambien in pregnancy. Consequently, we have not adopted your 12-4-92 proposed modifications for this section.]

Teratogenic effects: Pregnancy Category B.

Studies to assess the effects of zolpidem on human reproduction and development have not been conducted.

Teratology studies were conducted in rats and rabbits.

In rats, adverse maternal and fetal effects occurred at 20 and 100mg base/kg and included dose related maternal lethergy and ataxia and a dose related trend to incomplete ossification of fetal skull bones. Underossification of various fetal bones indicates a delay in maturation and is often seen in rats treated with sedative/hypnotic drugs. There were no teratogenic effects after zolpidem administration. The no effect dose for maternal or fetal toxicity was 4mg base/kg or 5 times the maximum human dose on a mg/m^2 basis.

In rabbits, dose related maternal sedation and decreased weight gain occurred at all doses tested. At the high dose, 16 mg base/kg, there was an increase in postimplantation fetal loss and underossification of sternebrae in viable fetuses. These fetal findings in rabbits are often secondary to reductions in maternal weight gain. There were no frank teratogenic effects. The no effect dose for fetal toxicity was 4mg base/kg or 7 times the maximum human dose on a mg/m^2 basis.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic effects: Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal

flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

Labor and Delivery

AMBIEN has no established use in labor and delivery.

Nursing Mothers

Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal volunteers (2.6 ± 0.3 hours). Between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown.

In addition, in a rat study, zolpidem inhibited the secretion of milk. The no effect dose was 4 mg base/kg or 6 times the recommended human dose in mg/m^2.

The use of AMBIEN in nursing mothers is not recommended.

Pediatric Use

Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from US trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%) and vomiting (0.5%).

Approximately 6% of 1,320 patients who received zolpidem at all doses (5 to 50 mg) in similar foreign trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.6%), amnesia (0.6%), dizziness (0.6%), headache (0.6%), and nausea (0.6%).

Incidence in Controlled Clinical Trials

Most Commonly Observed Adverse Events in Controlled Trials - During short term treatment (up to 10 nights) with AMBIEN at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo treated patients were: drowsiness

(reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer term treatment (28-35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo treated patients were: dizziness (5%), and drugged feelings (3%).

Adverse Events Observed at an Incidence of >1% in Controlled Trials

The tables below enumerate treatment emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received AMBIEN in U.S. placebo-controlled trials. Events reported by investigators were classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

The following table was derived from a pool of 11 placebo controlled short term U.S. efficacy trials involving zolpidem in doses ranging from 1.25 to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

INCIDENCE OF TREATMENT EMERGENT ADVERSE EXPERIENCES IN SHORT TERM PLACEBO-CONTROLLED CLINICAL TRIALS
(Percentage of Patients Reporting)

Body System Adverse Event*	Zolpidem (≤ 10 mg) (N=685)	Placebo (N=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Gastrointestinal System		
Nausea	2	3
Diarrhea	1	-
Musculoskeletal System		
Myalgia	1	2

*Events reported by at least 1% of AMBIEN patients are included.

The following table was derived from a pool of three placebo controlled long term efficacy trials involving AMBIEN. These trials involved patients with chronic insomnia who were treated for 28-35 nights with zolpidem at doses of 5, 10 or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse events occurring at an incidence of at least 1% for zolpidem patients.

INCIDENCE OF TREATMENT EMERGENT ADVERSE EXPERIENCES
IN LONG TERM PLACEBO-CONTROLLED CLINICAL TRIALS
(Percentage of Patients Reporting)

Body System/Placebo Adverse Event*	Zolpidem (≤ 10 mg) (N=152)	Placebo (N=161)
Autonomic Nervous System		
Dry Mouth	3	1
Body as a Whole		
Allergy	4	1
Back Pain	3	2
Influenza-like Symptoms	2	-
Chest Pain	1	-
Fatigue	1	2
Cardiovascular System		
Palpitation	2	-
Central and Peripheral Nervous System		
Headache	19	22
Drowsiness	8	3
Dizziness	5	1
Lethargy	3	1
Drugged Feeling	3	-
Light-Headed	2	1
Depression	2	1
Abnormal Dreams	1	-
Amnesia	1	-
Anxiety	1	1
Nervousness	1	3
Sleep Disorder	1	-
Gastrointestinal System		
Nausea	6	6
Dyspepsia	5	6
Diarrhea	3	2
Abdominal Pain	2	2
Constipation	2	1
Anorexia	1	1
Vomiting	1	1
Immunologic System		
Infection	1	1
Musculoskeletal System		
Myalgia	7	7
Arthralgia	4	4
Respiratory System		
Upper Respiratory Infection	5	6

Sinusitis	4	2
Pharyngitis	3	1
Rhinitis	1	3
Skin and Appendages		
Rash	2	1
Urogenital System		
Urinary Tract Infection	2	2

+Events reported by at least 1% of patients treated with AMBIEN.

Dose-Relationship for Adverse Events - There is evidence from dose comparison trials suggesting a dose-relationship for many of the adverse events associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Adverse Event Incidence Across the Entire Pre-approval Database

AMBIEN was administered to 3,021 subjects in clinical trials throughout the U. S., Canada and Europe. Treatment emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms. The frequencies presented, therefore, represent the proportions of the 3,021 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo controlled studies, those coding terms that are so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with AMBIEN, they were not necessarily caused by it.

> [We have made the slight modification to this paragraph suggested in your 12-4-92 draft.]

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Autonomic Nervous System: Infrequent: increased sweating, pallor, postural hypotension Rare: altered saliva, flushing, glaucoma, hypotension, impotence, syncope, tenesmus

Body as a Whole: Infrequent: asthenia, edema, falling, fever, malaise, trauma Rare: allergic reaction, allergy aggravated, abdominal body sensation, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease

Cardiovascular System: Infrequent: Cerebrovascular disorder, hypertension, tachycardia Rare: Arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia

Central and Peripheral Nervous System: Frequent: ataxia, confusion, euphoria, insomnia, vertigo Infrequent: agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, migraine, paraesthesia, sleeping (after daytime dosing), stupor, tremor Rare: abnormal thinking, aggressive reaction, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypotonia, hysteria, illusion, intoxicated feeling, leg cramps, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastro-Intestinal System: Infrequent: constipation, dysphagia, flatulence, gastroenteritis, hiccup, Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries

Hematologic and Lymphatic System: Rare: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura

Immunologic System: Rare: abscess, herpes simplex, herpes zoster, otitis externa, otitis media

Liver and Biliary System: Infrequent: increased SGPT Rare: abnormal hepatic function, bilirubinemia, increased SGOT

Metabolic and Nutritional: Infrequent: hyperglycemia Rare: gout, hypercholesteremia, hyperlipidemia, increased BUN, periorbital edema, thirst, weight decrease

Musculoskeletal System: Infrequent: arthritis Rare: arthrosis, muscle weakness, sciatica, tendinitis

Reproductive System: Infrequent: menstrual disorder, vaginitis Rare: breast fibroadenosis, breast neoplasm, breast pain

Respiratory System: Infrequent: bronchitis, coughing, dyspnea Rare: bronchospasm, epistaxis, hypoxia, laryngitis, pneumonia

Skin and Appendages: Rare: acne, bullous eruption, dermatitis, furunculosis, injection site inflammation, photosensitivity reaction, urticaria

Special Senses: Frequent: diplopia, vision abnormal Infrequent: eye irritation, scleritis, taste perversion, tinnitus Rare: corneal ulceration, eye pain, lacrimation abnormal, photopsia

Urogenital System: Infrequent: cystitis, urinary incontinence Rare: acute renal failure, dysuria, micturition frequency, polyuria, pyelonephritis, renal pain, urinary retention

DRUG ABUSE AND DEPENDENCE

[We have made the slight modifications to this section suggested in your 12-4-92 draft, and added a slight modification of our own.]

Ambien tablets have not yet been scheduled.

Abuse and Dependence

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The U.S. clinical trial experience from zolpidem does not reveal any clear evidence for a withdrawal syndrome. Nevertheless, the following adverse events included in DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependency, or the relationship of any dependency to dose and duration of treatment.

Because individuals with a history of addiction to, or abuse of, drugs or alcohol are at risk of habituation and dependence, they should be under careful surveillance when receiving zolpidem or any other hypnotic.

OVERDOSAGE

Signs and Symptoms - In European post-marketing reports of overdose with zolpidem alone, impairment of consciousness has ranged from somnolence to light coma. There was one case each of cardiovascular and respiratory compromise. Individuals have fully recovered from zolpidem tartrate overdoses up to 400 mg (40 times the maximum recommended dose). Overdose cases involving multiple CNS depressant agents, including zolpidem, have resulted in more severe symptomatology, including fatal outcomes.

Recommended Treatment - General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdosage, even if excitation occurs. The value of dialysis in the treatment of overdosage has not been determined, although hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

Poison Control Center - As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a Poison Control Center for up-to-date information on the management of hypnotic drug product overdosage.

DOSAGE AND ADMINISTRATION

The dose of Ambien should be individualized.

The recommended dose for adults is 10 mg immediately before bedtime.

Downward dosage adjustment may be necessary when Ambien is administered with agents having known CNS depressant effects because of the potentially additive effects.

Elderly or debilitated patients may be especially sensitive to the effects of Ambien. Patients with hepatic insufficiency do not clear the drug as rapidly as normals. An initial 5 mg dose is recommended in these patients (see PRECAUTIONS).

The total Ambien dose should not exceed 10 mg.

HOW SUPPLIED

Ambien 5 mg tablets are capsule-shaped, pink, film-coated, identified with markings of "SN 5" on one side and "5401" on the other and supplied as:

NDC Number	Size
0025-5401-31	bottle of 100
0025-5401-51	bottle of 500
0025-5401-34	carton of 100 unit dose in blister paks

Ambien 10 mg tablets are capsule-shaped, white, film-coated, identified with markings of "SN 10" on one side and "5421" on the other and supplied as:

NDC Number	Size
0025-5421-31	bottle of 100
0025-5421-51	bottle of 500
0025-5421-34	carton of 100 unit dose in blister paks

Store below 86°F (30°C)

Caution: Federal law prohibits dispensing without prescription.

END OF LABELING

[We have modified the following paragraph as suggested in your 12-4-92 draft.]

The text of the patient information for Ambien is set forth below.

Doc AMBENLAB.AP2

[In your 12-4-92 draft, you proposed a number of additional modifications to the PPI. Most of these modifications are acceptable, and we have incorporated them into this final draft of the PPI. However, 3 proposed changes were not acceptable. In particular, we have not added language recommending against use of Ambien during pregnancy, since as discussed earlier, we do not believe there is sufficient evidence for contraindicating such use. In addition, we have not added the sentence under 'Special Concerns' suggesting that none of these special problems are common for Ambien. There are insufficient data to support such a broad statement.]

INFORMATION FOR PATIENTS TAKING AMBIEN

Your doctor has prescribed AMBIEN to help you sleep. The following information is intended to guide you in the safe use of this medicine. It is not meant to take the place of your doctor's instructions. If you have any questions about AMBIEN tablets be sure to ask your doctor or pharmacist.

AMBIEN is used to treat different types of sleep problems, such as:

- trouble falling asleep
- waking up too early in the morning
- waking up often during the night

Some people may have more than one of these problems.

AMBIEN belongs to a group of medicines known as the "sedative/hypnotics," or simply, sleep medicines. There are many different sleep medicines available to help people sleep better. Sleep problems are usually temporary, requiring treatment for only a short time, usually 1 or 2 days up to 1 or 2 weeks. Some people have chronic sleep problems that may require more prolonged use of sleep medicine. However, you should not use these medicines for long periods without talking with your doctor about the risks and benefits of prolonged use.

SIDE EFFECTS

Most Common Side Effects

All medicines have side effects. Most common side effects of sleep medicines include:

- drowsiness
- dizziness
- lightheadedness
- difficulty with coordination

You may find that these medicines make you sleepy during the day. How drowsy you feel depends upon how your body reacts to the medicine, which sleep medicine you are taking, and how large a dose your doctor has prescribed. Day-time drowsiness is best avoided by taking the lowest dose possible that will still help you to sleep at night. Your doctor will work with you to find the dose of AMBIEN that is best for you.

To manage these side effects while you are taking this medicine:

- When you first start taking AMBIEN or any other sleep medicine until you know whether the medicine will still have some carryover effect in you the next day, use extreme care while doing anything that requires complete alertness, such as driving a car, operating machinery, or piloting an aircraft .
- NEVER drink alcohol while you are being treated with AMBIEN or any sleep medicine. Alcohol can increase the side effects of AMBIEN or any other sleep medicine.
- Do not take any other medicines without asking your doctor first. This includes medicines you can buy without a prescription. Some medicines can cause drowsiness and are best avoided while taking AMBIEN.
- Always take the exact dose of AMBIEN prescribed by your doctor. Never change your dose without talking to your doctor first.

SPECIAL CONCERNS

There are some special problems that may occur while taking sleep medicines.

Memory Problems

Sleep medicines may cause a special type of memory loss or "amnesia". When this occurs, a person may not remember what has happened for several hours after taking the medicine. This is usually not a problem since most people fall asleep after taking the medicine.

Memory loss can be a problem, however, when sleeping medicines are taken while traveling, such as during an airplane flight and the person wakes up before the effect of the medicine is gone. This has been called "traveler's amnesia".

Memory problems are not common while taking AMBIEN. In most instances, memory problems can be avoided if you take AMBIEN only

when you are able to get a full night's sleep (7 to 8 hours) before you need to be active again. Be sure to talk to your doctor if you think you are having memory problems.

Tolerance

When sleep medicines are used every night for more than a few weeks, they may lose their effectiveness to help you sleep. This is known as "tolerance". Sleep medicines should, in most cases, be used only for short periods of time, such as 1 or 2 days and generally no longer than 1 or 2 weeks. If your sleep problems continue, consult your doctor, who will determine whether other measures are needed to overcome your sleep problems.

Dependence

Sleep medicines can cause dependence, especially when these medicines are used regularly for longer than a few weeks or at high doses. Some people develop a need to continue taking their medicines. This is known as dependence or "addiction."

When people develop dependence, they may have difficulty stopping the sleep medicine. If the medicine is suddenly stopped, the body is not able to function normally and unpleasant symptoms (see "Withdrawal") may occur. They may find they have to keep taking the medicine either at the prescribed dose or at increasing doses just to avoid withdrawal symptoms.

All people taking sleep medicines have some risk of becoming dependent on the medicine. However, people who have been dependent on alcohol or other drugs in the past may have a higher chance of becoming addicted to sleep medicines. This possibility must be considered before using these medicines for more than a few weeks.

If you have been addicted to alcohol or drugs in the past, it is important to tell your doctor before starting AMBIEN or any sleep medicine.

Withdrawal

Withdrawal symptoms may occur when sleep medicines are stopped suddenly after being used daily for a long time. In some cases, these symptoms can occur even if the medicine has been used for only a week or two.

In mild cases, withdrawal symptoms may include unpleasant feelings. In more severe cases, abdominal and muscle cramps, vomiting, sweating, shakiness, and rarely, seizures may occur. These more severe withdrawal symptoms are very uncommon.

Another problem that may occur when sleep medicines are stopped is known as "rebound insomnia". This means that a person may

have more trouble sleeping the first few nights after the medicine is stopped than before starting the medicine. If you should experience rebound insomnia, do not get discouraged. This problem usually goes away on its own after one or two nights.

If you have been taking AMBIEN or any other sleep medicine for more than 1 or 2 weeks, do not stop taking it on your own. Always follow your doctor's directions.

Changes in Behavior and Thinking

Some people using sleep medicines have experienced unusual changes in their thinking and/or behavior. These effects are not common. However, they have included:

- more outgoing or aggressive behavior than normal
- loss of personal identity
- confusion
- strange behavior
- agitation
- hallucinations
- worsening of depression
- suicidal thoughts

How often these effects occur depends on several factors, such as a person's general health, the use of other medicines, and which sleep medicine is being used. Clinical experience with AMBIEN suggests that it is uncommonly associated with these behavior changes.

It is also important to realize that it is rarely clear whether these behavior changes are caused by the medicine, an illness, or occur on their own. In fact, sleep problems that do not improve may be due to illnesses that were present before the medicine was used. If you or your family notice any changes in your behavior, or if you have any unusual or disturbing thoughts, call your doctor immediately.

Pregnancy

Sleep medicines may cause sedation of the unborn baby when used during the last weeks of pregnancy.

Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, or if you become pregnant while taking AMBIEN.

SAFE USE OF SLEEPING MEDICINES

To ensure the safe and effective use of AMBIEN or any other sleep medicine, you should observe the following cautions:

1. AMBIEN is a prescription medicine and should be used ONLY as directed by your doctor. Follow your doctor's instructions about how to take, when to take, and how long to take AMBIEN.

2. Never use AMBIEN or any other sleep medicine for longer than directed by your doctor.

3. If you notice any unusual or disturbing thoughts or behavior during treatment with AMBIEN or any other sleep medicine, contact your doctor.

4. Tell your doctor about any medicines you may be taking, including medicines you may buy without a prescription. You should also tell your doctor if you drink alcohol. DO NOT use alcohol while taking AMBIEN or any other sleep medicine.

5. Do not take AMBIEN or any other sleep medicine unless you are able to get a full night's sleep before you must be active again. For example, AMBIEN or any other sleep medicine should not be taken on an overnight airplane flight of less than 7 to 8 hours since "traveler's amnesia" may occur.

6. Do not increase the prescribed dose of AMBIEN or any other sleep medicine unless instructed by your doctor.

7. When you first start taking AMBIEN or any other sleep medicine until you know whether the medicine will still have some carryover effect in you the next day, use extreme care while doing anything that requires complete alertness, such as driving a car, operating machinery, or piloting an aircraft .

8. Be aware that you may have more sleeping problems the first night or two after stopping AMBIEN or any other sleep medicine.

9. Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, or if you become pregnant while taking AMBIEN.

10. As with all prescription medicines, never share AMBIEN or any other sleep medicine with anyone else. Always store AMBIEN or any other sleep medicine in the original container out of reach of children.

11. AMBIEN works very quickly. You should only take AMBIEN right before you are going to bed and are ready to go to sleep.

SET 51

52 No.

4382938

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

Whereas, THERE HAS BEEN PRESENTED TO THE

Commissioner of Patents and Trademarks

A PETITION PRAYING FOR THE GRANT OF LETTERS PATENT FOR AN ALLEGED NEW AND USEFUL INVENTION THE TITLE AND DESCRIPTION OF WHICH ARE CONTAINED IN THE SPECIFICATION OF WHICH A COPY IS HEREUNTO ANNEXED AND MADE A PART HEREOF, AND THE VARIOUS REQUIREMENTS OF LAW IN SUCH CASES MADE AND PROVIDED HAVE BEEN COMPLIED WITH, AND THE TITLE THERETO IS, FROM THE RECORDS OF THE PATENT AND TRADEMARK OFFICE IN THE CLAIMANT(S) INDICATED IN THE SAID COPY, AND WHEREAS, UPON DUE EXAMINATION MADE, THE SAID CLAIMANT(S) IS (ARE) ADJUDGED TO BE ENTITLED TO A PATENT UNDER THE LAW.

NOW, THEREFORE, THESE Letters Patent ARE TO GRANT UNTO THE SAID CLAIMANT(S) AND THE SUCCESSORS, HEIRS OR ASSIGNS OF THE SAID CLAIMANT(S) FOR THE TERM OF SEVENTEEN YEARS FROM THE DATE OF THIS GRANT, SUBJECT TO THE PAYMENT OF ISSUE FEES AS PROVIDED BY LAW, THE RIGHT TO EXCLUDE OTHERS FROM MAKING, USING OR SELLING THE SAID INVENTION THROUGHOUT THE UNITED STATES.

In testimony whereof *I have hereunto set my hand and caused the seal of the* **Patent and Trademark Office** *to be affixed at the City of Washington this tenth day of May in the year of our Lord one thousand nine hundred and eighty-three, and of the Independence of the United States of America the two hundred and seventh.*

Attest:

Priscilla H Miller

Attesting Officer.

Commissioner of Patents and Trademarks.

United States Patent [19]

Kaplan et al.

[11] **4,382,938**

[45] **May 10, 1983**

[54] **IMIDAZO[1,2-A] PYRIDINE DERIVATIVES AND THEIR APPLICATION AS PHARMACEUTICALS**

[75] Inventors: **Jean-Pierre Kaplan**, Bourg la Reine; **Pascal George**, Vitry sur Seine, both of France

[73] Assignee: **Synthelabo**, Paris, France

[21] Appl. No.: **313,601**

[22] Filed: **Oct. 21, 1981**

[30] **Foreign Application Priority Data**

Oct. 22, 1980 [FR] France 80 22537

[51] Int. Cl.³ **A61K 31/435**; C07D 471/04

[52] U.S. Cl. **424/256**; 544/58.4; 544/127; 544/362; 546/121

[58] Field of Search 544/58.4, 127, 362; 546/121; 424/246, 248.54, 250, 248.52, 256

[56] **References Cited**

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1076089 7/1967 United Kingdom .

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Almirante et al., II, J. Med. Chem., vol. 12, (1969) pp. 123–126.

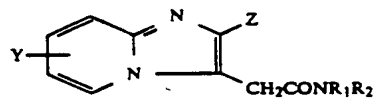
Primary Examiner—Henry R. Jiles

Assistant Examiner—Bernard Dentz

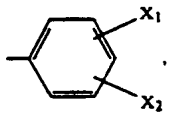
Attorney, Agent, or Firm—Wegner & Bretschneider

[57] **ABSTRACT**

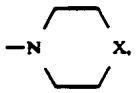
Imidazo[1,2-a] pyridines of the formula:



and their acid addition salts in which Y represents a hydrogen or halogen atom or a C_{1-4} alkyl radical, Z represents a naphthyl radical or a radical



in which each of X_1 and X_2 independently of one another is a hydrogen or halogen atom, a C_{1-4} alkoxy radical, a C_{1-6} alkyl radical or CF_3, CH_3S—, CH_3SO_2—, —NO_2, —NH_2 or —$NHCOCH_3$, and each of R_1 and R_2 independently of one another represents a hydrogen atom, a straight or branched C_{1-5} alkyl radical which is unsubstituted or substituted by one or more halogen atoms or hydroxyl, —$N(C_{1-4}$ alkyl$)_2$, carbamoyl or C_{1-4} alkoxy radicals, allyl, propargyl, a C_{3-6} cycloalkyl radical, benzyl, or phenyl, not both R_1 and R_2 being hydrogen, or —NR_1R_2 represents a heterocyclic ring containing from 3 to 6 carbon atoms, or a heterocyclic ring of the formula



in which X is O, S, CHOR' or >N—R, R' being hydrogen or benzyl and R being hydrogen, a C_{1-4} alkyl radical, or phenyl which is unsubstituted or substituted by methoxy or a halogen atom, which may be made from the corresponding acids, have valuable pharmacological properties, especially anxiolytic, anti-anoxic, sleep-inducing, hypnotic and anticonvulsant properties.

12 Claims, No Drawings

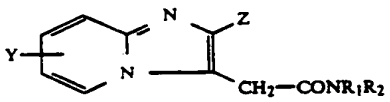
IMIDAZO[1,2-a] PYRIDINE DERIVATIVES AND THEIR APPLICATION AS PHARMACEUTICALS

DESCRIPTION

The present invention relates to imidazo [1,2-a] pyridine derivatives, useful in therapy and their preparation.

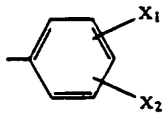
Imidazo [1,2-a] pyridines have already been described in the literature, for example in British Pat. Nos. 991,589 and 1,076,089 and in various other publications.

The compounds of the present invention have the formula (I)

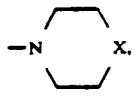


(I)

in which Y represents a hydrogen or halogen atom or a C_{1-4} alkyl radical, Z represents a naphthyl radical or a radical

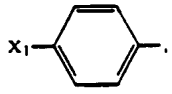


in which each of X_1 and X_2 independently of one another is a hydrogen or halogen atom, a C_{1-4} alkoxy radical, a C_{1-6} alkyl radical or CF_3, CH_3S, CH_3SO_2 or NO_2 and each of R_1 and R_2 independently of one another represents a hydrogen atom, a straight or branched C_{1-5} alkyl radical which is unsubstituted or substituted by one or more halogen atoms, hydroxyl, $N(C_{1-4}alkyl)_2$, carbamoyl or C_{1-4} alkoxy radicals, an allyl radical, a propargyl radical, a C_{3-6} cycloalkyl radical, a benzyl radical or a phenyl radical, not both R_1 and R_2 being hydrogen, or NR_1R_2 represents a heterocyclic ring containing from 3 to 6 carbon atoms, or a heterocyclic ring of the formula,



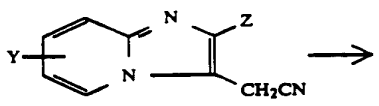
in which X is O, S, CHOR' or >NR, R' being hydrogen or benzyl and R being hydrogen, a C_{1-4} alkyl radical or phenyl which is unsubstituted or substituted by methoxy or a halogen atom.

The preferred compounds of the invention are those in which R_1 and R_2 are both alkyl radicals. Amongst these compounds, those in which Y is in the 6-position and represents either a halogen atom or the methyl radical are particularly preferred. Finally, amongst the latter compounds, there may be mentioned those in which Z is a radical

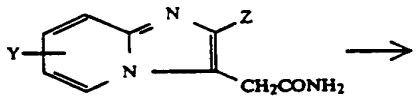


in which X_1 is a halogen atom or the radical CH_3.

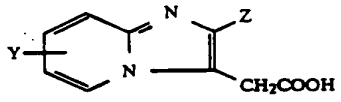
According to a feature of the invention, the compounds of formula (I) can be prepared according to the following reaction scheme:



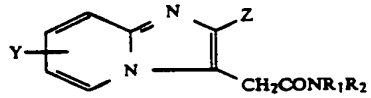
(II)



(III)



(IV)



(I)

The reaction for the conversion of the nitrile (II) to the primary amide is carried out in accordance with a conventional method, for example with the aid of an acid such as dry hrdrogen chloride, in a solvent such as formic acid, at a temperature from 15° to 50° C.

The saponification of the primary amide (III) to the acid (IV) may be carried out in ethanolic potassium hydroxide at the reflux temperature.

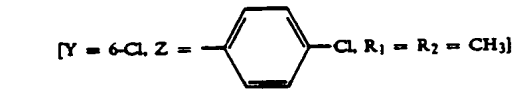
The conversion of the acid (IV) to the amide compound of formula (I) is carried out in accordance with any suitable method, for example by reacting the acid (IV) with the amine HNR_1R_2, in the presence of carbonyldiimidazole, or by reacting the chloride of the acid (IV) with the amine HNR_1R_2.

The general method for the preparation of the starting nitriles (II) is described in the literature, in particular in British Pat. No. 1,076,089.

The following Examples illustrate the present invention. The analyses and the IR and NMR spectra confirm the structure of the compounds.

EXAMPLE 1

6-Chloro-2-(4-chlorophenyl)-imidazo[1,2-a]-pyridine-3-N, N-dimethylacetamide.



[Y = 6-Cl, Z = —Cl, $R_1 = R_2 = CH_3$]

1. 22 g (0.0788 mol) of 6-chloro-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine-3-acetonitrile are added to 85 ml of 99% formic acid and the solution is treated with a stream of dry hydrogen chloride for 3 to 4 hours. When all the nitrile has been converted, the solution is heated

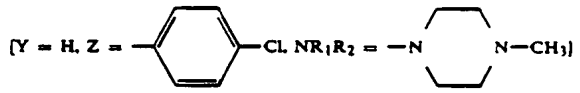
slightly to degas it, and the cooled solution is then poured into 1 liter of water; the mixture is stirred for 10 minutes and then rendered alkaline with 200 ml of concentrated ammonia solution. The solid is filtered off, washed copiously with water and dried under a water-pump vacuum. The 6-chloro-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine-3-acetamide is recrystallised from ethanol. Melting point = 285°-7° C.

2. 19.2 g of 6-chloro-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine-3-acetamide and 19 g of KOH are added successively to 550 ml of 75% ethanol. The suspension is heated at the reflux temperature for 10–16 hours. When the reaction has ended, the solution is concentrated in vacuo and the residue is dissolved in ½ liter of water. The small amount of insoluble material is filtered off and the filtrate is treated with 50 ml of acetic acid. The expected acid precipitates and it is filtered of and roughly dried. The crude product is taken up in 500 ml of acetone and the 6-chloro-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine-3-acetic acid is filtered off hot. Melting point = 258°–260° C.

3. 4 g (12.45 millimols) of 6-chloro-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine-3-acetic acid and 2.42 g (14.94 millimols) of carbonyldiimidazole are suspended in 60 ml of dry tetrahydrofuran. The reaction mixture is stirred at 20° C. until the evolution of carbon dioxide has ended, and is then heated gently at 40° C. for 15 minutes and cooled to 0° C. A solution of 14.94 millimols of dimethylamine in 5 ml of tetrahydrofuran is then added. The suspension is stirred for 15 minutes at 20° C. and then concentrated; the residue is treated with 300 ml of water and 50 ml of a saturated aqueous solution of $NaHCO_3$. The insoluble material is filtered off, washed with water and dried. The compound obtained is recrystallised from a solvent such as ethanol. Melting point = 230° C.

EXAMPLE 2

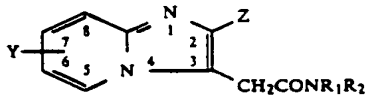
4-Methyl-1{[2-(4-chlorophenyl)-imidazo[1,2-a]pyridin-3-yl]methylcarbonyl}-piperazine.



4.5 g (15.64 millimols) of 2-(4-chlorophenyl)-imidazo[1,2-a]pyridine-3-acetic acid are added to a suspension of N,N-dimethyl-chloro-methyleneiminium chloride prepared by adding 2.2 g (17.75 millimols) of oxalyl chloride to 30 ml of dimethylformamide (DMF) at −10° C. The suspension is stirred for 15 minutes at 0° C. and a solution of 5.4 g (54 millimols) of 4-methylpiperazine in 10 ml of dry DMF is then added gradually thereto at 0° C. The solution is stirred for 8 hours and then poured into 750 ml of water. The amide is extracted with CH_2Cl_2, the organic phase is dried over Na_2SO_4 and concentrated, the residue is passed through a silica column (eluant: CH_2Cl_2/CH_3OH 9/1) and the compound obtained is recrystallised from an isopropyl ether/acetonitrile mixture. Melting point = 175° C.

The compounds listed in the following Table were similarly prepared.

TABLE



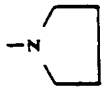
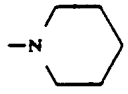
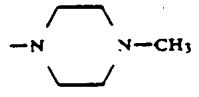
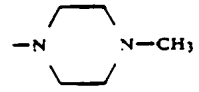
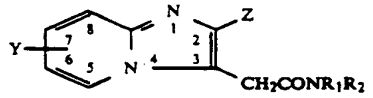
Compound	Y	Z	NR_1R_2	Melting point (°C.)
1	H	4-Cl—C_6H_4	—$NHCH_3$	234
2	H	4-Cl—C_6H_4	—$N(CH_3)_2$	179
3	H	4-Cl—C_6H_4		187–8
4	H	4-Cl—C_6H_4		190
5	H	4-Cl—C_6H_4		175
6	H	3-CF_3—C_6H_4		157.5–158

TABLE-continued



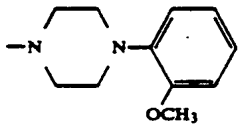
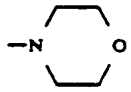
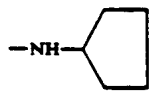
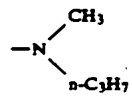
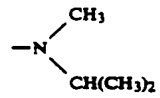
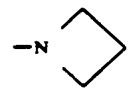
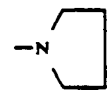
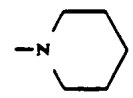
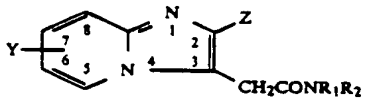
Compound	Y	Z	NR_1R_2	Melting point (°C.)
7	H	4-Cl—C_6H_4		206–7
8	H	4-Cl—C_6H_4		242
9	6-Cl	4-Cl—C_6H_4	—$NHCH_3$	>290
10	6-Cl	4-Cl—C_6H_4	—NHC_2H_5	280–2
11	6-Cl	4-Cl—C_6H_4	—NH—n-C_3H_7	229–30
12	6-Cl	4-Cl—C_6H_4	—NH—i-C_3H_7	259
13	6-Cl	4-Cl—C_6H_4	—NH—n-C_4H_9	225
14	6-Cl	4-Cl—C_6H_4	—NH—t-C_4H_9	224
15	6-Cl	4-Cl—C_6H_4		243–5
16	6-Cl	4-Cl—C_6H_4	—NHC_6H_5	265–7
17	6-Cl	4-Cl—C_6H_4	—$NHCH_2C_6H_5$	253–4
18	6-Cl	4-Cl—C_6H_4	—$NHCH_2CH_2OH$	260–1
19	6-Cl	4-Cl—C_6H_4	—$NHCH_2CH_2OCH_3$	197
20	6-Cl	4-Cl—C_6H_4	—$NHCH_2CH_2N(CH_3)_2$	199–201
21	6-Cl	4-Cl—C_6H_4	—$NHCH_2CH{=}CH_2$	233
22	6-Cl	4-Cl—C_6H_4	—$NHCH_2—C{\equiv}CH$	239
23	6-Cl	4-CH_3—C_6H_4	—NHC_2H_5	238
24	6-Cl	4-Cl—C_6H_4	—$NHCH_2CF_3$	258
25	6-Cl	4-Cl—C_6H_4	—$NHCH_2CONH_2$	256–7
26	6-Cl	4-Cl—C_6H_4	—$N(CH_3)_2$	230
27	6-Cl	4-Cl—C_6H_4	—$N(C_2H_5)_2$	149
28	6-Cl	4-Cl—C_6H_4	—N(n-C_3H_7)$_2$	140–1
29	6-Cl	4-Cl—C_6H_4		160
30	6-Cl	4-Cl—C_6H_4		185–6
31	6-Cl	4-Cl—C_6H_4	—N(n-C_4H_9)$_2$	149–150
32	6-Cl	4-Cl—C_6H_4		243–5
33	6-Cl	4-Cl—C_6H_4		219–220
34	6-Cl	4-Cl—C_6H_4		208–9

TABLE-continued



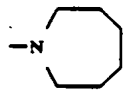
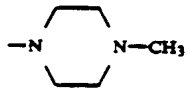
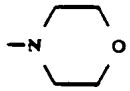
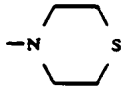
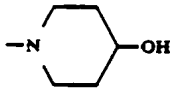
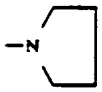
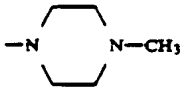
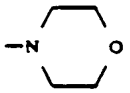
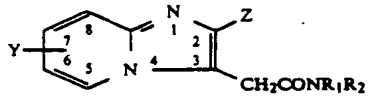
Compound	Y	Z	NR_1R_2	Melting point (°C.)
35	6-Cl	4-Cl—C_6H_4		190–2
36	6-Cl	4-Cl—C_6H_4		>300
37	6-Cl	4-Cl—C_6H_4		204–6
38	6-Cl	4-Cl—C_6H_4		262
39	6-Cl	4-Cl—C_6H_4		239–241
40	6-Cl	4-Cl—C_6H_4		270
41	6-CH_3	4-Cl—C_6H_4	—$NHCH_3$	261–2
42	6-CH_3	4-Cl—C_6H_4	—NHC_2H_5	224–5
43	6-CH_3	4-Cl—C_6H_4	—NH—CH_2CH_2OH	246
44	6-CH_3	4-Cl—C_6H_4	—$N(CH_3)_2$	215
45	6-CH_3	4-Cl—C_6H_4	—NH—CH_2—CH_2—Cl	202
46	6-CH_3	4-Cl—C_6H_4		194
47	6-Cl	C_6H_5	—$NHCH_3$	276–7
48	6-Cl	C_6H_5	—$N(CH_3)_2$	192
49	6-Cl	4-CH_3—C_6H_4	—$NHCH_3$	277–8
50	6-Cl	4-CH_3—C_6H_4	—$N(CH_3)_2$	185–6
51	6-Cl	4-CH_3O—C_6H_4	—$NHCH_3$	273
52	6-Cl	4-CH_3O—C_6H_4	—$N(CH_3)_2$	166
53	6-Cl	4-Br—C_6H_4	—NHC_2H_5	287
54	6-Cl	4-Br—C_6H_4	—$N(C_2H_5)_2$	168
55	6-Cl	naphth-2-yl		217–8
56	6-Cl	naphth-2-yl		193–4
57	6-Cl	naphth-1-yl	—$N(CH_3)_2$	187–8
58	6-Cl	2-CH_3—C_6H_4	—$NHCH_3$	175–6
59	6-Cl	2-CH_3—C_6H_4	—NHC_2H_5	161–2
60	6-Cl	2-CH_3O—C_6H_4	—NHC_2H_5	172–3

TABLE-continued



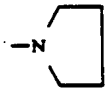
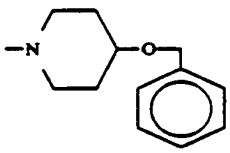
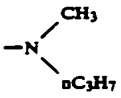
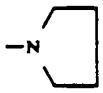
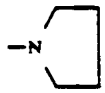
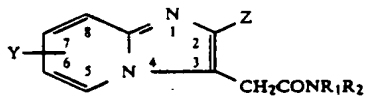
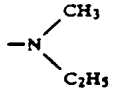
Compound	Y	Z	NR_1R_2	Melting point (°C.)
61	6-Cl	3-Cl—C_6H_4	—NHC_2H_5	215–6
62	6-Cl	3-CH_3O—C_6H_4	—$N(C_2H_5)_2$	98–9
63	6-Cl	3-CH_3O—C_6H_4		190
64	6-Cl	3,4-Cl_2—C_6H_3	—$N(CH_3)_2$	221–2
65	6-Cl	3,4-$(CH_3O)_2$—C_6H_3	—$N(CH_3)_2$	215
66	6-Cl	3,4-$(CH_3O)_2$—C_6H_3	—$N(n\text{-}C_3H_7)_2$	147
67	7-CH_3	4-Cl—C_6H_4	—NHC_2H_5	228
68	7-CH_3	4-Cl—C_6H_4	—$N(CH_3)_2$	206
69	8-CH_3	4-Cl—C_6H_4	—$NHCH_3$	234
70	8-CH_3	4-Cl—C_6H_4	—$N(C_2H_5)_2$	175.5
71	6-Cl	4-F—C_6H_4	—$N(CH_3)_2$	210
72	6-Cl	4-F—C_6H_4	—$N(n\text{-}C_4H_9)_2$	129
73	6-CH_3	4-F—C_6H_4	—$N(CH_3)_2$	195
74	6-Cl	4-Br—C_6H_4	—$N(CH_3)_2$	228–9
75	6-CH_3	4-CH_3—C_6H_4	—$N(CH_3)_2$	196
76	6-CH_3	4-Cl—C_6H_4	—$N(n\text{-}C_4H_9)_2$	116
77	6-Cl	4-Cl—C_6H_4		152
78	H	4-Cl—C_6H_4	—$N(n\text{-}C_3H_7)_2$	136
79	H	4-Cl—C_6H_4	—$N(n\text{-}C_4H_9)_2$	105
80	6-Cl	4-Cl—C_6H_4	—$N(n\text{-}C_5H_{11})_2$	92–3
81	6-CH_3	4-CH_3—C_6H_4	—$NHCH_3$	187
82	6-CH_3	4-CH_3—C_6H_4	—NHC_2H_5	184
83	6-CH_3	4-$CH_3C_6H_4$		108
84	6-CH_3	4-$CH_3C_6H_4$	—$N(n\text{-}C_3H_7)_2$	115
85	6-CH_3	4-CH_3—C_6H_4		168
86	6-CH_3	4-Cl—C_6H_4	—$NHCH_2CF_3$	239
87	6-CH_3	4-Br—C_6H_4	—NHC_2H_5	232–4
88	6-CH_3	4-Br—C_6H_4	—$N(CH_3)_2$	203.5–205
89	6-CH_3	4-Br—C_6H_4	—$N(n\text{-}C_3H_7)_2$	138–9
90	6-CH_3	4-Br—C_6H_4		195.5–197
91	6-CH_3	4-CH_3O—C_6H_4	—$N(CH_3)_2.CH_3SO_3H$	230–2
92	6-CH_3	4-CH_3S—C_6H_4	—$N(CH_3)_2.CH_3SO_3H$	209
93	6-CH_3	4-CH_3SO_2—C_6H_4	—$N(CH_3)_2$	227–9
94	6-CH_3	4-NO_2—C_6H_4	—NHC_2H_5	268–270
95	6-CH_3	4-NO_2—C_6H_4	—$N(CH_3)_2$	262–3
96	6-CH_3	4-t-C_4H_9—C_6H_4	—$N(CH_3)_2$	199–200

TABLE-continued



Compound	Y	Z	NR_1R_2	Melting point (°C.)
97	6-Cl	4-Cl—C_6H_4		173

The compounds of the invention were subjected to pharmacological experiments which showed their valuable pharmacological properties in various areas.

The toxicity of the compounds was determined on mice by intraperitoneal administration. The LD 50 ranges from 500 to 1,000 mg/kg.

The anxiolytic activity was determined according to the eating test (R. J. Stephens, (1973), Brit. J. Pharmac., 49, 146 P). In this test, the doses which increases the food consumption of the mice vary from 0.1 to 10 mg/kg, administered intraperitoneally.

The activity of the compounds in the area of cerebral circulation was determined in the test for the hypoxia caused by pressure reduction. Mice of the CD1 strain are kept in an oxygen-depleted atmosphere produced by creating a partial vacuum (190 mm of mercury, corresponding to 5.25% of oxygen). The survival time of the animals is noted. This time is increased by agents which are capable of assisting the oxygenation of tissues and in particular of the brain. The compounds studied are administered intraperitoneally in several doses, 10 minutes before the experiment. The percentage increases in the survival time, relative to the values obtained for control animals, are calculated. The mean active dose (MAD), that is to say the dose which increases the survival time by 100%, is determined graphically. The MAD ranges from 0.3 to 32 mg/kg, administered intraperitoneally.

The anticonvulsant activity was determined in accordance with the test for the antagonism towards the mortality induced by bicuculline in mice (P. Worms, H. Depoortere and K. G. Lloyd, (1979) Life Sci., 25, 607–614). The products to be studied are injected intraperitoneally, 30 minutes before the bicuculline (0.9 mg/kg, administered intravenously). With death being the criterion selected for this test, the percentage mortalities are noted for each batch, 2 hours after administration of the bicuculline (control batch: 100% mortality). For each product, the 50% active dose (AD 50 or the dose which protects 50% of the animals from the lethal effects of the bicuculline) is determined graphically. The AD 50 of the compounds of the invention vary between 0.3 and 30 mg/kg, administered intraperitoneally.

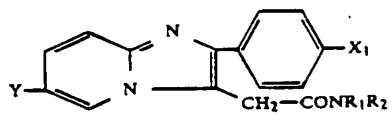
The sedative or hypnotic activity was determined by observing the action of the compounds on the EEG of curarised rats and also on the wake-sleep states in freely moving, implanted rats and cats (H. Depoortere, Rev. E.E.G. Neurophysiol., (1980) 10, 3, 207–214; L. M. Da Costa, H. Depoortere and R. Naquet, Rev. E.E.G. Neurophysiol., (1977), 7, 2, 158–164). In curarised rats, the products to be studied were injected intraperitoneally or orally at doses increasing from 0.1 to 30 mg/kg. They induce sleep traces starting from doses ranging from 0.1 to 10 mg/kg, administered intraperitoneally or orally. In freely moving, implanted rats, the products to be studied were injected intraperitoneally or orally at a single dose ranging from 1 to 10 mg/kg. At these doses, they reduce the total wake time by 13 to 44%, without significantly changing the total paradoxical sleep time, certain products even increasing the total duration of this phase of sleep. In freely moving, implanted cats, the products to be studied were injected intraperitoneally or orally at a single dose of 10 mg/kg. They transitorily increase the wake time after injection, this being accompanied by benzodiazepine-type jactation, and reduce the total paradoxical sleep time by 40 to 100%. However, certain products increase the total duration of the SWSP (slow-wave sleep with phase phenomena: P.G.O. points) by about 50%.

The results of these various tests show that the compounds of the invention possess anxiolytic, anti-anoxic, sleep-inducing, hypnotic and anticonvulsant propertis; the compounds of the invention are useful for the treatment o anxiety states, sleep disorders and other neurological and psychiatric complaints, for the treatment of vigilance disorders, in particular for combating behavioural disorders which can be attributed to cerebral vascular damage and to the cerebral sclerosis encountered in geriatrics, and also for the treatment of epileptic vertigo due to cranial traumatisms and for the treatment of metabolic encephalopathies.

The compounds of the invention can be presented in any form which is suitable for oral or parenteral administration, for example in the form of tablets, coated tablets, capsules, solutions to be taken orally or injected, and the like, with any suitable excipient. The daily posology can range from 0.5 to 2,000 mg.

What is claimed is:

1. A compound of the formula



wherein

X_1 is halogen or methyl;

Y is hydrogen, halogen or methyl;

R_1 is hydrogen, C_{1-5} alkyl or hydroxy (C_{1-5} alkyl); and

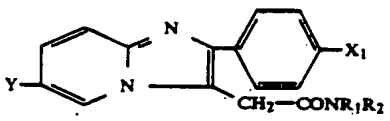
R_2 is C_{1-5} alkyl or hydroxy (C_{1-5} alkyl)

or a pharmaceutically acceptable salt thereof.

2. An imidazo[1,2-a]pyridine according to claim 1, in which R_1 and R_2 are both alkyl radicals.

3. An imidazo[1,2-a]pyridine according to claim 2, in which Y is chlorine or methyl.

4. A method of providing a patient with a hypnotic effect which comprises administerinng to said patient a hypnotically-effective amount of a compound of the formula:



wherein

X_1 is halogen or methyl;

Y is hydrogen, halogen or methyl;

R_1 is hydrogen, C_{1-5} alkyl or hydroxy (C_{1-5} alkyl); and

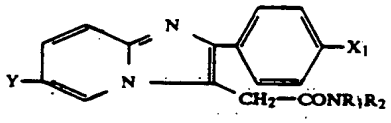
R_2 is C_{1-5} alkyl or hydroxy (C_{1-5} alkyl)

or a pharmaceutically acceptable salt thereof.

5. A method of claim 4 wherein R_1 and R_2 are alkyl.

6. A method of claim 5 wherein Y is chlorine or methyl.

7. A method of providing a patient with an anxiolytic effect which comprises administering to said patient an anxioloytically-effective amount of a compound of the formula:



wherein

X_1 is halogen or methyl;

Y is hydrogen, halogen or methyl;

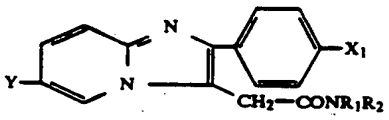
R_1 is hydrogen, C_{1-5} alkyl or hydroxy (C_{1-5} alkyl); and

R_2 is C_{1-5} alkyl or hydroxy (C_{1-5} alkyl) or a pharmaceutically acceptable salt thereof.

8. A method of claim 7 wherein R_1 and R_2 are alkyl.

9. A method of claim 8 wherein Y is chlorine or methyl.

10. A method of providing a patient with an anticonvulsive effect which comprises administering to said patient an anticonvulsive dosage of a compound of the formula:



wherein

X_1 is halogen or methyl;

Y is hydrogen, halogen or methyl;

R_1 is hydrogen, C_{1-5} alkyl or hydroxy (C_{1-5} alkyl); and

R_2 is C_{1-5} alkyl or hydroxy (C_{1-5} alkyl) or a pharmaceutically acceptable salt thereof.

11. A method of claim 10 wherein R_1 and R_2 are alkyl.

12. A method of claim 11 wherein Y is chlorine or methyl.

* * * * *

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BOX M. FEE

Jean-Pierre KAPLAN et al.

Serial No. : 313,601

284 1620
REEL FRAME

Filed : October 21, 1981

U.S. Patent No. : 4,382,938

Issued : May 10, 1983

Title : IMIDAZO[1,2-A] PYRIDINE DERIVATIVES AND THEIR APPLICATION AS PHARMACEUTICALS

PAYMENT OF SEVEN AND A-HALF YEAR MAINTENANCE FEE

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

Attached hereto is a check for $495.00 in payment of the maintenance fee due within seven years and six months after the original grant. This payment is calculated in accordance with 37 CFR 1.20(e), as the application on which this patent issued was filed before August 27, 1982

Should this check become detached or any fee adjustment be necessary, kindly credit or debit our Deposit Account No. 23-0783 as necessary.

Please forward the maintenance fee receipt to the undersigned at the fee address noted at the bottom of this order for payment.

Respectfully submitted,

WEGNER, CANTOR, MUELLER & PLAYER

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Attorney Docket No. HCW-18524-P
October 24, 1990
HAW:KLB:rgm/mf5

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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WEGNER & BRETSCHNEIDER
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DATE MAILED
11/23/90

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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	S
1	4,662,044	173	490	----	06/851,867	05/05/87	04/11/86	04	NO	P
2	4,666,272	273	245	----	06/785,959	05/19/87	10/10/85	04	YES	P
3	4,664,615	173	490	----	06/804,764	05/12/87	12/05/85	04	NO	P
4	4,382,938	171	495	----	06/313,601	05/10/83	10/21/81	08	NO	P
5	4,663,298	273	245	----	06/691,007	05/05/87	01/14/85	04	YES	P

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	HCW-18844-A
2	P112-85084
3	HIC-19425-A
4	HCW18524
5	DPM-19119

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTOL-439 (REV 1-88)